Drug use in population screening. Pharmacoepidemiological and pharmacoeconomical aspects

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DRUG USE IN
A POPULATION SCREENING

Pharmacoepidemiological and
Pharmacoeconomical Aspects

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To my parents,

my brothers and sisters

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CHAPTER 1

General Introduction

Microalbuminuria, a slightly elevated urinary albumin excretion (UAE), is a marker for early vascular endothelial damage [1] and indicative for an increased glomerular permeability [2]. Studies so far show that microalbuminuria is independently associated with increased risks of cardiovascular and renal disease in diabetic patients [3-5], hypertensive subjects [6-11] as well as in the general population [12-18].

Microalbuminuria is a predictor of cardiovascular events

A 10 year observational follow-up study of 939 adults with type 1 diabetes from the Steno Diabetes Centre showed that microalbuminuria is related to a higher cardiovascular risk (relative risk 1.45; 95% CI 1.18-1.77) [3;4]. Most attention has been paid to describe the association between microalbuminuria and cardiovascular risk in patients with type 2 diabetes. In a meta-analysis, Dinnen and Gerstein demonstrated a twofold increased risk of all-cause mortality and cardiovascular morbidity and mortality associated with microalbuminuria in patients with type 2 diabetes [5].

In patients with essential hypertension, microalbuminuria predicts cardiovascular disease. In the recently performed LIFE study among 8206 hypertensive patients with left ventricular hypertrophy, increased urinary albumin-to-creatinine ratio (UACR) was shown to be associated with an increased risk of cardiovascular morbidity and mortality [10]. Albuminuria in essential hypertension may reflect systemic dysfunction of the vascular endothelium, a structure intimately involved in permeability, haemostasis, fibrinolysis, and blood pressure control [19].

The last few years, increased evidence has become available on the relation between microalbuminuria and cardiovascular events in high-risk populations as well as in the general population at large. In the HOPE study [5], 9643 participants with either a history or an increased risk of cardiovascular disease (CVD) were followed prospectively for 4.5 years. It was shown that microalbuminuria significantly increased relative risk of major new cardiovascular events (myocardial infarction, stroke or cardiovascular death), all cause death and hospitalization for congestive heart failure by almost twofold for each endpoint. The largest population-based study examining the predictive role of urinary albumin excretion on cardiovascular and renal morbidity and mortality, the PREVEND study [13] included more than 40,000 participants. A doubling of urinary albumin concentration was associated with a 29% increased risk of mortality CVD and 12% increased risk of dying from non-CVD causes after adjusting for other

covariates. The Norway HUNT study [15] showed the presence of microalbuminuria was associated with a twofold increased risk of all-cause mortality in 2089 apparently healthy individuals without diabetes or hypertension. In the much larger EPIC-Norfolk study [17], which included more than 20,000 British men and women, microalbuminuria was associated with a 50% increase in relative risk of all-cause mortality and more than a doubling in the risk of cardiovascular mortality.

Microalbuminuria is a predictor of renal function impairment

Several studies have indicated that microalbuminuria is also a marker of glomerular damage, and strongly predicts the development of overt proteinuria and progressive renal failure in patients with insulin or non insulin dependent diabetes mellitus (IDDM or NIDDM) [20-26] . Recently, evidence has been published suggesting that the predictive value of microalbuminuria for renal damage may extend to patients with essential hypertension [9,27]. Hypertensive patients with microalbuminuria manifest a greater decline in renal function than patients with normal UAE. This confirms the observation of Ruilope et al [28], who observed a decline in GFR of 11 ml/min in 24 hypertensive patients with microalbuminuria compared with a decrease of only 2ml/min in hypertensive patients with normal UAE. In the general population, it has also been shown that albuminuria predicts renal function loss [29].

Screening for albuminuria

As discussed, microalbuminuria may predict cardiovascular disease and renal function outcome in subjects with or without diabetes or hypertension [29]. Therefore, microalbuminuria might be a target for detection of vascular dysfunction. In that respect, screening on albuminuria may be a useful tool to identify subjects at risk for CVD and/or progressive renal failure [30;31]. However, the question remains which populations, either high risk only or the general population, should be chosen for screening. The answer to this question will amongst others depend on the cost effectiveness of such screening programs. A recent study showed that screening for dipstick proteinuria via the general practitioner with subsequent angiotensin converting enzyme inhibitor treatment of patients who were positive, was not cost effective in preventing end stage renal disease (ESRD) [32]. One should realize, however that treatment of patients with albuminuria will prevent ESRD only in the long run, but will potentially prevent

cardiac events much earlier. Incorporation in the analysis of reduced cardiovascular morbidity and mortality, in addition to ESRD, might improve the cost effectiveness of screening and treatment for albuminuria. Also in persons without hypertension or diabetes, in whom such intervention was previously found not cost-effective, cost-effectiveness may improve to favourable ratios. Furthermore, screening for albuminuria will result in a much higher yield of patients at risk than screening for dipstick proteinuria. Finally, screening may be cheaper to perform when carried out via health offices or postal submission than via the general practitioner [30;33].

Treatment of albuminuria

Several classes of drugs have been reported to be associated with urinary albumin excretion (UAE), such as drugs which are prescribed in patients with hypertension, hypercholesteremia or diabetes. Data from recent intervention studies suggest that treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), offers significant reduction in progression to overt proteinuria and renal function decline. Moreover, ACE-inhibitor or ARB intervention resulted in reduction of cardiovascular and renal morbidity in people with albuminuria [26, 34-36]. In the HOPE study of performed in 9243 patients who had vascular disease or diabetes, treatment with ramipril 10 mg significantly reduced the incidence of the composite outcome of myocardial infarction, stroke or death from cardiovascular disease in normoalbuminuric, but especially in the microalbuminuric subgroup [37]. Similarly, the PREVEND-IT [38] study showed that in microalbuminuric patients, treatment with fosinopril had a significant effect on urinary albumin excretion. In addition, fosinopril treatment was associated with a trend in reducing cardiovascular events. In the LIFE study, reduction in albuminuria explained one-fifth of the benefits of losartan versus atenolol with respect to cardiovascular morbidity and mortality [39]. In view of these findings, it has recently been suggested that albuminuria is not only a risk marker for cardiovascular and renal disease but may be a useful target for therapy [40].

Other studies showed that cholesterol lowering drugs had a renal protective effect. Human data mostly report a statin induced lowering of UAE in patients with advanced renal disease [41] and in type 2 diabetic patients with microalbuminuria [42], but no change [43] or even an increase in albuminuria has also been described [44;45]. In a short term cross-sectional study, Monster et al could not confirm that statins are associated with a lower prevalence of microalbuminuria [46]. Other drugs that may influence the level of urinary albumin excretion are

hormonal contraceptives. Hormonal contraceptives (HC) are suggested to induce a rise in blood pressure (BP) and urinary albumin excretion (UAE), while the effect of HC on renal function (GFR) is still in debate [47-49]. Monster et al [50] described in a cross-sectional study that the use of hormonal contraceptives may be associated with an increased risk for albuminuria, independent of blood pressure. However, data on long-term effects of HC-use and withdrawal effects of HC-use on these outcomes are not available.

Screening and drug prescribing

Strategies to reduce cardiovascular and renal morbidity and mortality are focused on a better detection of the risk factor and improving the proportion of patients receiving adequate treatment. Screening and treatment of cardiovascular and renal risk factors such as hypertension, hyperlipidemia and albuminuria can reduce the incidence of cardiovascular and renal events [31;51;52].

However, little is known yet about negative consequences of a screening program for cardiovascular and renal risk factors in primary prevention. The assumption is that the benefits of early diagnosis in asymptomatic individuals will outweigh any possible harm associated with screening, diagnosis and treatment. Some have argued against the screening because such programs may result in medicalisation [53-55].

Aim of the thesis

The first objective of this thesis is to explore the pharmaco-epidemiological aspects of a population-based screening on albuminuria. Firstly, we questioned the effect of such a population-based screening as well as the effect of an intervention letter to the general practitioner on drug prescribing. Secondly, we assessed the effect of drug use (statin and hormonal contraceptives) on UAE and renal function.

The second objective of this thesis is to know the pharmacoeconomic aspects of a population-based screening on albuminuria. For this purpose, firstly we investigated the adherence of pharmacoeconomic studies in the Netherlands to the national guidelines for health-economics research. Secondly, based on the PREVEND data, we calculated the cost-effectiveness of screening and subsequent treatment of albuminuria to prevent cardiovascular and renal events.

This thesis used data of the Prevention of Renal and Vascular ENd-stage Disease (PREVEND) cohort study and PREVEND Intervention Trial, and linked

both data sources to the InterAction Database (IADB) for the information on drug use.

The PREVEND study

The PREVEND study was designed to prospectively investigate the natural course of increased levels of urinary albumin excretion and its relation to renal and cardiovascular disease in a large cohort drawn from the general population. Details of this study have been described elsewhere [50]. In summary (figure-1), in the period 1997 to 1998, all inhabitants of the city of Groningen, the Netherlands, aged between 28-75 years, were sent a questionnaire and a vial to collect an early morning urine sample (N=85,421). Of these subjects, 40,856 responded (47.8%) and sent a vial to a central laboratory where urinary albumin and creatinine concentrations were measured. After exclusion of subjects with type 1 DM (defined as the use of insulin) and pregnant women, all subjects with a urinary albumin concentration (UAC) of ≥10 mg/L (N=6000) and a randomly selected control group with UAC <10 mg/L (N=2592) were invited for further investigations in an outpatient clinic and to collect two consecutive 24-hour urines. These 8592 subjects constitute the PREVEND cohort. They were invited for a second screening after a mean follow-up of 4.2 years (range 2.8-6.1). By then 246 subjects had died, 130 were lost to follow-up and 1322 declined participation, leaving 6,894 subjects who completed the second screening. The pharmacy data of the PREVEND participants are available from the InterAction DataBase (IADB).

The PREVEND Intervention Trial (PREVEND IT)

To prove that lowering of urinary albumin excretion is possible, and that such treatment will also result in an improved renal and cardiovascular outcome, the PREVEND Intervention Trial was conducted as randomized trial nested within the observational PREVEND study.

The PREVEND IT aimed to study the effect of fosinopril and pravastatin on cardiovascular outcome. The protocol of this study has been described in detail elsewhere [38]. In short, 864 of the 8,592 subjects participating in the PREVEND were included in this clinical trial (figure-1). Inclusion criteria were a UAE of 15-300 mg/d, a blood pressure less than 160/100 mmHg without use of antihypertensive, and plasma cholesterol <8.0 mmol/L, or <5.0 mmol/L in case of previous myocardial infarction and without the use of lipid lowering agents. These 864 subjects were treated in a double blind, randomised, placebo-controlled trial

according to a 2x2 factorial design with fosinopril 20 mg / day or matching placebo and with pravastatin 40 mg / day or matching placebo during four years.

The InterAction DataBase (IADB)

The IADB contains pharmacy-dispensing data from community pharmacies in the city of Groningen. Dutch patients usually register at a single community pharmacy and therefore this pharmacy can provide an almost complete listing of subject's prescribed drugs [57]. Pharmacy data contain, among others, information on the name of drug prescription, number of days the drug was prescribed and the number of defined daily dose (DDDs) based on definition of WHO [58]. The use of over the counter (OTC) drugs and in-hospital prescriptions are not included. Information on drug use of the PREVEND participants was collected from at least one year prior to the date of the first screening until at least the second screening.

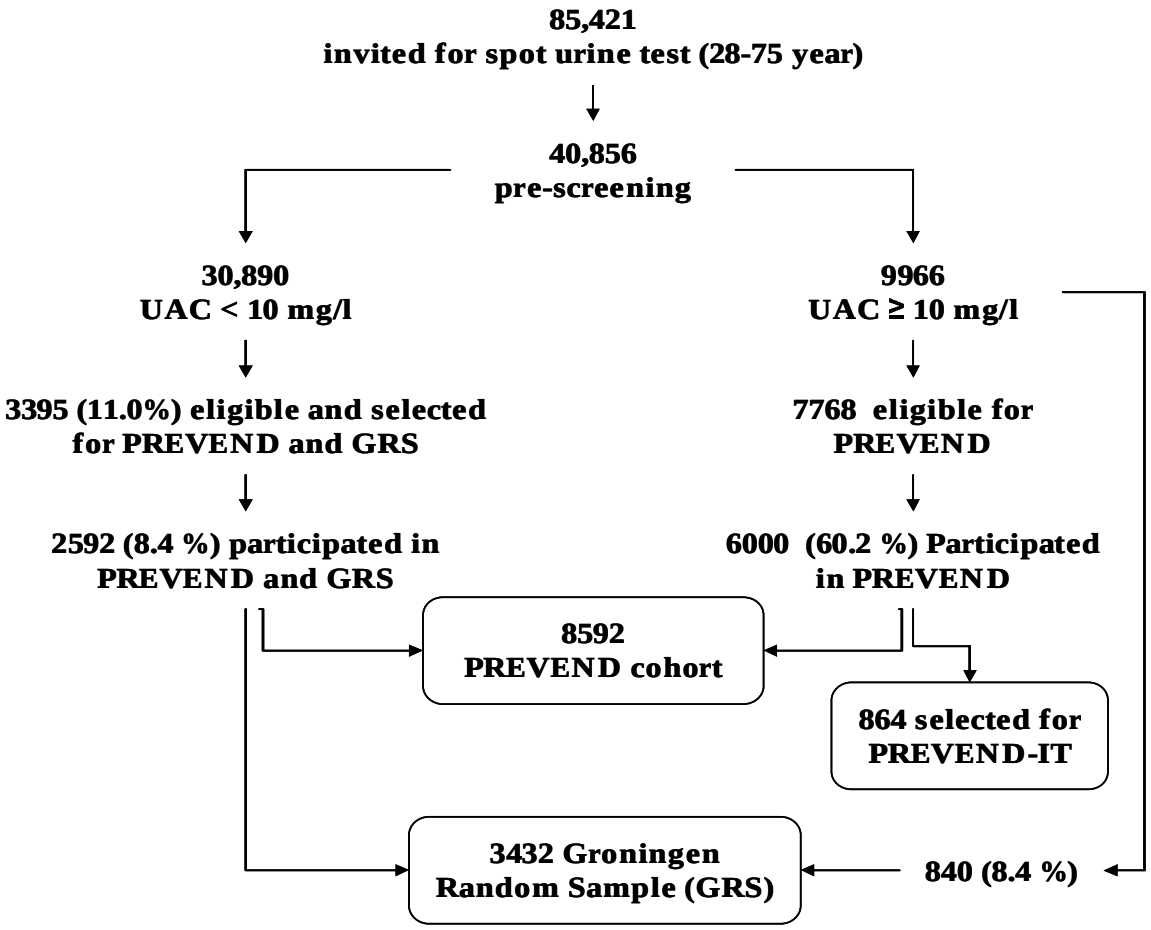

***Figure 1**. Flowchart of PREVEND and PREVEND-IT study*

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CHAPTER 2

The effect of hypertension and hypercholesterolemia screening with subsequent intervention letter on the use of blood pressure and lipid lowering drugs.

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ABSTRACT

Introduction

To evaluate the effect of a letter intervention that was send to both the participants of a population screening and their general practitioners. We also tested what predicting variables influenced the GP to actually prescribe blood pressure lowering drugs (BPLD) or lipid lowering drugs (LLD).

Methods

The study design was an observational follow-up study, in PREVEND outpatient clinic in Groningen University Hospital, The Netherlands. We used the clinical data of the 8592 subjects that participated in the first screening of the PREVEND study. Data on drug use was collected from community pharmacies. Drug use was measured the year before and after the screening with the subsequent intervention letter. As control population without intervention, we used the data from the InterAction DataBase (IADB) standardized for the population characteristics of the intervention group. The letter intervention was sent to participants who had shown after screening to have either an elevated blood pressure or plasma cholesterol, and the letter contained the advice to use a BPLD or LLD. Main outcome measures were proportion of patients prescribed BPLD and/or LLD in the year before and after the intervention, and variables that influence the GP to prescribe BPLD and LLD.

Results

Data from the community pharmacy were available from 7567 (88%) subjects. 397 participants (5.2%) received a letter with advice to start a BPLD, and 326 participants (4.3%) received a letter with advice to start a LLD. The prevalence of patients who were using BPLD and LLD before the intervention was not significantly different between the intervention and control group, 16.6 (CI 95% 15.8-17.5) *vs* 16.0 and 4.8 (4.4-5.3) *vs* 4.6 respectively. After the letter intervention, the prevalence of BPLD use was higher in the intervention group compared with the control group (19.4 [18.5-20.3] *vs* 17.0%), as was the prevalence of LLD use (7.1 [6.5-7.7) *vs* 5.4%). The same held true for the incidence of BPLD (3.4 [3.0-3.8] *vs* 2.5%) and LLD use (2.1 [1.8-2.4] *vs* 1.0%), respectively, in the year after the intervention. Univariate and multivariate analysis showed that a higher blood pressure and cholesterol level, but not the presence of other cardiovascular risk factors, were associated to with a greater percentage use of a BPLD and a LLD.

Conclusions

A population survey followed by a letter of intervention to both the patient and GP are effective to improve the use of blood pressure and lipid lowering drugs as a primary prevention in patients with hypertension and hyperlipidemia. Our therapeutic advice however, was followed only in about one of the three subjects with hypertension and one of the four subjects with hyperlipidemia. The levels of blood pressure and plasma total cholesterol are important variables influencing the GP to prescribe a BPLD and / or LLD.

INTRODUCTION

Hypertension and hyperlipidemia occur relatively frequent and are important risk factors for cardiovascular morbidity and mortality. These risk factors can be detected easily, and effective treatment is available [1-4]. Moreover, treatment of hypertension and hyperlipidemia reduces cardio- and cerebrovascular event rates [5-7]. However, hypertension is still frequently undiagnosed and/or untreated or inadequately treated [8-9]. Strategies to reduce the cardiovascular risk of hypertension and hyperlipidemia are focused on a better detection of the risk factor, and on improving the proportion of patients receiving adequate treatment [1,4,5].

At present many programs aim to detect the presence of cardiovascular risk factors via population screening. However, how often is detection followed by the start of active treatment with adequate follow up of the subject at risk? Little attention is paid to the way the participant and his/her general practitioner should be motivated to start adequate risk factor treatment. Various intervention strategies are being applied to influence prescription behavior with the goal to obtain a higher proportion of patients receiving treatment [10]. These interventions are targeted to either the patients, the general practitioners/health provider, or both [11-12]. The letter also can be used as intervention to improving drug use [13-16]. An intervention letter is relatively inexpensive, acceptable and successful at delivering the message.

The objective of this study is to evaluate the effect of a letter intervention that was sent to both the participants of a population screening and their general practitioners. Furthermore, we studied which factors influence the general practitoner to prescribe blood pressure or lipid lowering drugs.

METHODS

Study design and population

This study is part of the ongoing PREVEND (Prevention of REnal and Vascular ENd stage Disease) study, a large part of population of Groningen (The Netherlands). We use clinical data of the first screening of the PREVEND study cohort that was performed in 1997/1998. This study has been described in detail elsewhere [17-18]. Briefly, PREVEND is designed to study the impact of microalbuminuria on cardiovascular and renal morbidity and mortality in the general population. Pregnant women and insulin using diabetic subjects were excluded. The cohort consists of 8592 subjects aged 28 to 75 years old.

Measurements

In these participants among others, body weight and length and blood pressure were measured. Also fasting blood was drawn for measurement of plasma glucose and cholesterol and two 24-hour urine samples were collected for measurement of urinary albumin excretion. All the participants also completed a questionnaire regarding demographics, smoking status, the use of blood pressure lowering, lipid lowering and oral antidiabetic drugs, the family history on cardiovascular disease, and the history on previous myocardial infarction and cerebrovascular accident.

Body weight was measured to the nearest 0.5 kg with Seca balance scale, after removal of shoes and heavy clothing. Height was measured to the nearest 0.5 cm using a statiometer with right angle. Body mass index (BMI) was calculated as weight (in kilogram) divided by the square of height (in meters). Systolic and diastolic blood pressure were measured on two separate occasions in supine position at the right arm every minute for 10 minutes with an automatic Dinamp XL Model 9300 series device. Blood pressure was calculated as the mean of the last two measurements of the two visits. Plasma total cholesterol and plasma glucose was measured by dry chemistry (Kodak Ectachem, Rochester, NY, USA). Urinary albumin concentration was determined by nephelometry (Dade Behring diagnostics, Marburg, Germany) with a threshold of 2.3 mg/l and intra- and inter-assay coefficients of variation of less than 2.2% and 2.6%, respectively.

Pharmacy data were collected when subjects gave permission to obtain that data from their community pharmacy. Drug use was collected for at least one year prior to the participant's visit to PREVEND outpatient unit, and for the year after that visit. The PREVEND study was approved by the local medical ethics committee and conducted according the guidelines of the declaration of Helsinki.

Definitions

Elevated blood pressure was defined as systolic blood pressure $\geq$ 160 mmHg or $\geq$ 95 mmHg for diastolic. Elevated plasma cholesterol was defined as total cholesterol $\geq$ 8 mmol/l or $\geq$ 5 mmol/l when the subjects had suffered a previous myocardial infarction. Subjects were classified as smokers if they reported current smoking or had stopped smoking less than one year before; otherwise, they were classified as nonsmokers. Subjects were defined to have experienced a myocardial infarction, cerebrovascular attack and family history of cardiovascular disease when they answered positively on the questionnaire. Definitions were described in detail elsewhere [17-18].

Intervention letters

In case the participant was found to have an elevated blood pressure or plasma cholesterol on the screening and had indicated on the questionnaire not to be treated with a BPLD and/or LLD, a formal letter signed by the head of PREVEND study was sent once to both the participant and his/her general practitioner. In the letter to the general practitioner, we informed them about the result of the screening (actual blood pressure and cholesterol level as well as the presence of an abnormal plasma glucose and urinary albumin excretion) and we advised to start either a BPLD and/or a LLD. We defined this group as the intervention group.

At the same time, we sent the letter to the patients. The letters encouraged the participants to go into contact with their general practitioner to discuss the result and to have the drug prescribed. The letter to the general practitioner informed him/her about the result of that individual participant and encouraged to start with a BPLD and/or LLD, although we clearly left the final decision to do so at the general practitioner.

The control group

We included a control group that was obtained from the InterAction DataBase (IADB), which contains pharmacy-dispensing data of a population of approximately 200.000 subjects. This database contains, among other things, the name of drug, the date the drugs were prescribed and ATC (Anatomical Therapeutical Chemical) code. The use of over the counter drugs and in-patient prescriptions are not included [19].

We studied the use of BPLDs or LLDs in this control (IADB) group one-year before and after July 1st 1998. The IADB contained data of 120,836 subjects between 28 to 75 years old in the year before and of 124,695 subjects of the same age in the year thereafter. As the age and sex distribution in the control population is different from the PREVEND population, we standardized and adjusted the subjects from IADB to the PREVEND age and sex distribution. Thus, we had a control population comparable in age and sex distribution to the intervention group. The study design can be seen in figure-1.

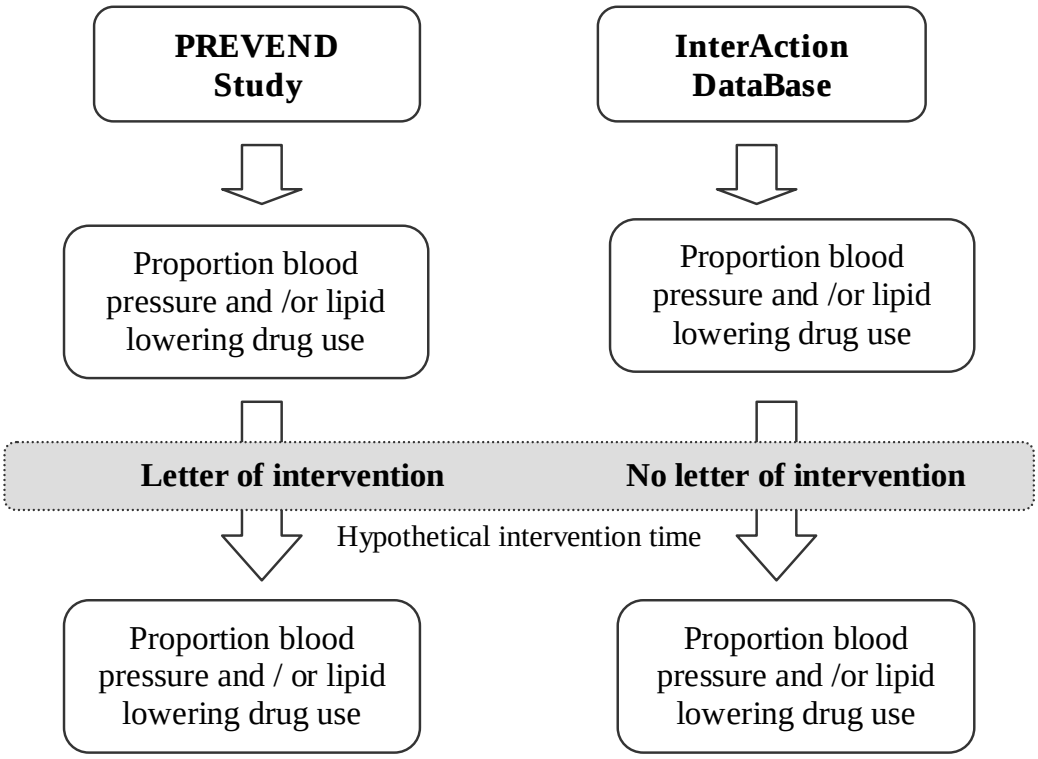

***Figure-1**. Flowchart of study letter of intervention for intervention group and control*

Statistical analysis

Analyses were performed using SPSS 11.0. and CIA (Confidence Interval Analysis) with Wilson Score Methods. Data are presented as number or mean with standard deviation for continuous variables and as percentage of column total for categorical variables. Differences in proportion were tested using chi-square or Fischer's exact test. A *p*-value <0.05 is considered statistically significant. All *p*-values are two tailed. Risk estimate of the dichotomous variables is performed odds ratio and 95% confidence interval, and continuous variables were tested by *t*-test.

Prevalence and incidence show the proportion of the patients using the drug. The prevalence include all patients who use a BPLD or LLD, while the incidence include the patients who start to use a BPLD or LLD after the intervention while not using a BPLD or LLD 1 year before the intervention or at least 180 days (for control group).

A logistic regression model was used to determine variables related to blood pressure or lipid lowering drug prescribing.

Table-1. *Characteristics of the PREVEND study population (N=7567), stratified by type of letter intervention*

	Received BPLD letter		**Received LLD letter**	
	Yes	**No***	**Yes**	**No***
N (%)	397 (5.2)	7170 (94.8)	326 (4.3)	7241 (95.7)
Male (%)	60.2	48.7	63.2	48.7
Age (years)	63.4 ± 8.2	48.7 ± 12.4	59.0 ± 10.8	49.1 ± 12.5
Systolic Blood Pressure (mmHg)	179.0 ± 13.7	126.4 ± 16.8	133.6 ± 16.3	129.0 ± 20.6
Diastolic Blood Pressure (mmHg)	91.1 ± 9.0	73.2 ± 9.0	76.4 ± 8.7	74.0 ± 9.9
Total cholesterol level (mmol/l)	6.1 ± 1.1	5.6 ± 1.1	7.6 ± 1.6	5.6 ± 1.0
Glucose level (mmol/l)	5.6 ± 1.8	4.9 ± 1.2	5.4 ± 1.8	4.9 ± 1.2
Body Mass Index (kg/m^2)	28.3 ± 4.3	26.0 ± 4.2	27.3 ± 3.7	26.1 ± 4.3
Median (25th-75th) UAC (mg/l)	27.6 (12.6-59.6)	9.2 (6.3-16.6)	13.3 (7.1-41.8)	9.5 (6.4-17.5)
Smoking (%)	33.6	45.3	46.4	44.6
Cardiovascular family history (%)	38.7	33.1	45.8	32.8
Cerebrovascular accident (%)	2.0	0.9	2.2	0.9
Myocardial infarction (%)	5.6	3.6	45.7	1.8

BPLD = blood pressure lowering drug; LLD = lipid lowering drug, UAC = urinary albumin concentration; All variables significant (p value <.05) different versus those that received a letter, except smoking

RESULTS

Comparison of the PREVEND groups that received or did not receive a letter

In the PREVEND study group, 1025 subjects out of the 8592 (11.9%) were excluded because no pharmacy data were available. Altogether, 7567 subjects were eligible for analysis. 397 Participants (5.2%) received the letter with an advice to start a blood pressure lowering drug (BPLD) and 326 participants (4.3%) received the letter with the advice to start a lipid lowering drug (LLD). Three patients received both letters; they have been included in both analyses. Baseline characteristics from these subjects according to predictor variables stratified by type of intervention letter are given in Table-1.

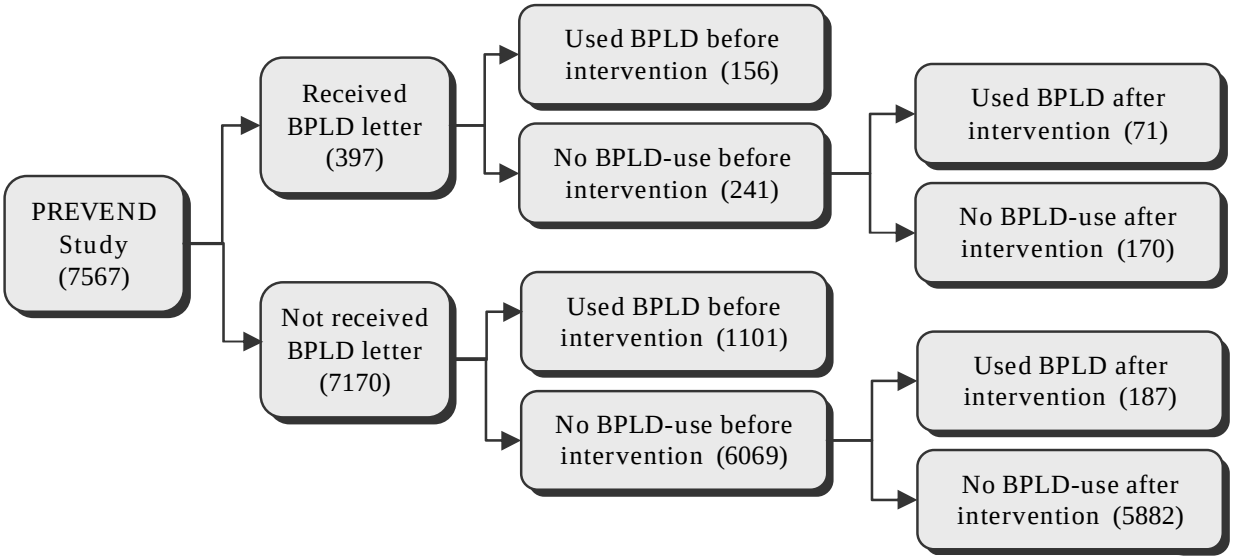

***Figure-2**. Patient flow on PREVEND Study and the Blood Pressure Lowering Drugs (BPLD) letter of intervention*

Blood pressure lowering drugs

156 Out of 397 (39.3%) participants who received a BPLD letter already appeared to use a BPLD according to the pharmacy data, and were thus inadequately treated (Figure-2). The other 241 that received such a BPLD letter were not using a BPLD before, and were thus correctly diagnosed as new hypertensive, that is 3.2% of the entire PREVEND cohort. 71 Out of these 241 participants (29.5%) started to use a BPLD, while the other 170 subjects (70.5%) did not. This indicates that we succeeded to reduce the percent of undiagnosed and untreated hypertension from 3.2 to 2.2%.

In the group of 7170 subjects that had not received a letter to start a BPLD, 1101 were using a BPLD already, and were thus adequately treated. Of the 6069 that were not using a BPLD before the screening, 187 (3.1%) started on blood pressure lowering therapy the year after the screening.

Lipid lowering drugs

Fifty-one out of the 326 (14%) participants who received a LLD letter appeared to be on such treatment already according to the pharmacy data, but were thus inadequately treated (Figure-3). The other 275 that received such a letter were not using a LLD before (3,6% of the entire PREVEND population). 73 Out of the 275 participants (26.5%) started to use a LLD, while the other 202 did not. Our screening with subsequent intervention letter resulted in reduction of undiagnosed and untreated hyperlipidemia of 3.6% to 2.7%.

In the group of 7241 subjects that had not received a letter to start a LLD, 341 were using such treatment already, and were thus adequately treated. Of the remaining 6927 who were not using a LLD before the screening, 86 (1.2%) started such therapy the year after the screening.

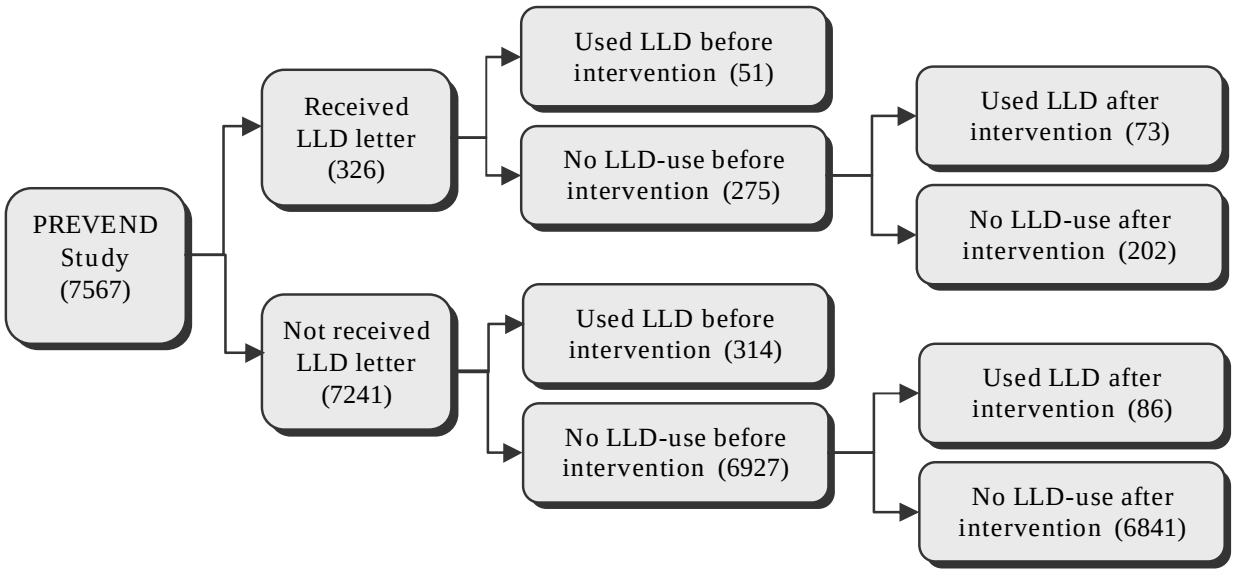

Figure-3*. Patient flow on PREVEND Study and the Lipid Lowering Drugs (LLD) letter of intervention*

Comparison of the PREVEND group and the control group

Table-2 indicates the figures on the prevalence of the use of BPLDs and LLDs in the year before and after the screening for both the PREVEND and the control population. According to the pharmacy data, 1257 of the 7579 PREVEND subjects (16.6%) used BPLD before the screening, which was not different from the prevalence of 16.0% the control population. The use of BPLDs had increased in the overall PREVEND cohort in the year after the screening to 19.4% (delta 2.8%), which was significantly higher than in the control group (17% [delta 1%]; $p<0.001$). The incidence of those who started BPLDs in the year after the screening, was higher in the overall PREVEND group *vs* the control (3.4 *vs* 2.5%; $p<0.001$).

Table-2*. Prevalence and incidence of BPLD or LLD use in the PREVEND study and control population before and after the letter of intervention*

	PREVEND (95% CI)	**IADB ***
Blood Pressure Lowering Drug (BPLD)		
Prevalence using BPLD before intervention	16.6 (15.8-17.5)	16.0
Prevalence using BPLD after intervention	19.4 (18.5-20.3)	17.0
Delta prevalence (after-before)	2.8	1.0
Incidence using BPLD	3.4 (3.0-3.8)	2.5
Lipid Lowering Drug (LLD)		
Prevalence using LLD before intervention	4.8 (4.4-5.3)	4.6
Prevalence using LLD after intervention	7.1(6.5-7.7)	5.4
Delta prevalence (after-before)	2.3	0.8
Incidence using LLD	2.1 (1.8-2.4)	1.0

** standardized by age and sex*

Similarly, 365 of the 7579 PREVEND subjects (4.8%) used lipid lowering treatment the year before the screening, which was not different from the prevalence in the control group (4.6%). The use of LLDs had increased in the overall PREVEND cohort in the year after the screening to 7.1% (delta 2.3%), which was significantly higher than in control group (5.4% (delta 0.8%); $p<0.001$). The incidence of LLD use in the year after the screening, was also higher in the PREVEND versus the control group (2.1 *vs* 1.0).

Table-3. *Univariate and multivariate analysis association between predictor variables and use of BPLD or LLD after the letter intervention*

	Odds ratio (95% Confidence Interval)			
	Use of BPLD		**Use of LLD**	
	Univariate	**Multivariate***	**Univariate**	**Multivariate***
Male (%)	1.32 (0.75-2.31)	-	1.09 (0.63-1.89)	-
Age (years)	0.99 (0.95-1.02)	-	0.99 (0.97-1.02)	-
Systolic Blood Pressure (mmHg)	1.04 (1.02-1.07) ‡	1.04 (1.02-1.07)	0.99 (0.97-1.00)	-
Diastolic Blood Pressure (mmHg)	1.05 (1.02-1.09) †	1.04 (1.00-1.07)	0.99 (0.96-1.02)	-
Total cholesterol level (mmol/l)	0.84 (0.65-1.10)	-	1.20 (1.00-1.43) *	1.25 (1.03-1.52)
Glucose level (mmol/l)	1.02 (0.87-1.20)	-	0.93 (0.79-1.10)	-
Body Mass Index (kg/m^2)	0.98 (0.91-1.04)	-	1.02 (0.95-1.09)	-
Albumin urine (mg/24hr)	1.00 (1.00-1.01)	-	1.00 (1.00-1.01)	-
Smoking (%)	0.68 (0.37-1.23)	-	1.37 (0.80-2.35)	-
Family history for cardiovascular disease (%)	1.33 (0.74-2.38)	-	1.12 (0.64-1.97)	-
Cerebrovascular accident (%)	4.97 (0.44-55.73)	-	0.54 (0.06-4.72)	-
Myocardial infarction (%)	1.49 (0.346-6.42)	-	0.73 (0.42-1.29)	-

*BPLD: Blood pressure lowering drug; LLD: Lipid lowering drug; ‡ p<0.001, † p<0.005, * p<0.05*

Variables influencing the decision to follow the therapeutic advice

Both univariate and multivariate analysis showed that the level of systolic and diastolic blood pressure contributed to the decision to start BPLDs after the intervention: the higher the blood pressure, the greater the chance that the subject used a BPLD the year after detection of the elevated pressure (Table-3). However, the presence of another cardiovascular risk factor did not contribute to the decision to start such treatment. With respect to the decision to start of a LLD we found in the analysis that only the level of plasma cholesterol, but not the level of blood pressure, neither the presence of other cardiovascular risk factors was associated with the use of a LLD the year thereafter.

DISCUSSION

We showed that the screening with subsequent intervention letter to participant and general practitioner resulted in a lowering of the percent of untreated hypertension and untreated hyperlipidemia compared with a control population. However, our therapeutic advice was only followed in about one of the three subjects with hypertension and in one of the four subjects with hyperlipidemia. In the decision to follow our advice, the general practitioner was influenced by the level of the risk factor itself, but not by the presence of other cardiovascular risk factors.

Before the screening, the prevalence of subjects using blood pressure and lipid lowering treatment was comparable in our PREVEND group as in the control group, standardized for age and sex. This indicates that the PREVEND cohort, although enriched for the presence of microalbuminuria, seems an adequate representation of the general population. The figure of about 16% for the use of BPLD and 5% for LLD are slightly higher compared to other reports in the Netherlands (10-13% for BPLD [20-21] and 2.3-3.5% for LLD) [22-23]. We found the number of new prescriptions for BPLD after the screening plus intervention letter about 35% higher than in the control group. This indicates that in our study group significantly more subjects started to use BPLD than in the control population. The number of new prescriptions for lipid lowering drugs in the PREVEND cohort was even more than twice that in the control population. Our data thus indicate that our approach of screening with the subsequent intervention letter is successful to

promote prescription behavior by the general practitioner. These data are in agreement with literature [13, 14]. Collins et al also showed that a letter intervention is effective to increase the number of prescriptions for dypiridamole [13]. Similarly, Rascati *et al.* found that an intervention letter to the general practitioner is effective to change prescribing behaviour [14]. In contrast, Feder *et al.* found that postal prompts to patients and their general practitioners about secondary prevention after myocardial infarction did not result in a significantly better use of lipid lowering agents and beta blockers [24]. However the number of patients in that study (n=328) may have been to small to detect a significant difference [25].

As far as we know, our study is the first that evaluates the effectiveness of an intervention letter in addition to a population screening. We informed both participant and general practitioner to start drug treatment. This prompted the participants to visit the general practitioner and to discuss the benefits and disadvantages of drug treatment for the established risk factor. Nevertheless, in a minority of the patients our advice to start treatment was followed, possibly due to the fact that the general practitioner in general is relatively reluctant to start drug treatment in asymptomatic subjects. Many practitioners still fail to take aggressive steps in lowering blood pressure if the patient is simply feeling well [26].

In this study we followed the criteria to start treatment according to the consensus of the general practitioners, which was at that time less strict than internationally accepted criteria (systolic pressure > 140 mmHg and diastolic pressure > 90 mmHg [27]). In light of this, the percentage that received drug treatment is disappointingly low. The international guidelines also advice to start drug treatment when other cardiovascular risk factors, such as diabetes, smoking, or a positive family history for cardiovascular disease are present [27-30] However, none of these factors were taken into account in the decision to start the treatment in our cohort. Only the level of the risk factor itself guided the decision, which is in accordance of data in the literature [31]. The finding that the treatment advice was less frequently followed in those who were smoking suggests that patient behaviour may be an important determinant of compliance to the advice to visit the general practitioner and to start BPLD.

Our study had some shortcomings. First, the PREVEND study population was enriched for the presence of microalbuminuria. However, the prevalence of using blood pressure and lipid lowering drugs before the intervention was not different from the control group. Moreover, the general practitioner did not seem influenced by the presence of microalbuminuria in his / her decision to start drug treatment. Second, we are not aware whether the patients used BPLDs for other reasons than hypertension, such as beta blocking drugs for angina, because the

IADB has no information on diagnosis. The same holds true for the control group and cannot explain the higher incidence of blood pressure lowering drug prescriptions in the PREVEND population than in the control group after the intervention letter. This moreover, cannot explain the increase in use of lipid lowering drugs that in fact are not prescribed for another indication than lipid lowering. Third, we only have a follow up of one year after the screening, and thus can not exclude that in some participant's drug treatment was started only afterwards. This is not unexpected, as the general practitioner may first have tried other non-drug approaches to correct the elevated risk factor. We also considered that probably some patients had a raised blood pressure when attending for the study visit which was subsequently lower when rechecked by the general practitioner. However if this is the case an underestimation should occur.

Our data seem robust, as we were able to compare the effect of our screening with subsequent intervention letter in the PREVEND cohort with the prescription pattern in a large cohort in the northern of the Netherlands. This seems a justified approach as the prescription behavior before the intervention appeared comparable in both cohorts. Our data moreover are not influenced by expectations from the general practitioner, as we collected the prescription data from the pharmacies, and not via the general practitioner. The pharmacist in fact was not informed on the letter that was sent to the participant and the general practitioners. An important approach in our design was the fact that we both informed the patient and general practitioner on the benefits of using drug treatment for the risk factor. This indeed, resulted in an increase in the visits of our participants to their general practitioner [32].

In conclusion, a screening of the general population on cardiovascular and renal risk factors with subsequent letter to intervene with drug treatment in hypertension and/or hyperlipidemia shows an increase in prescribing, although definitely not optimal. The level of blood pressure and plasma cholesterol, but not the presence of other cardiovascular risk factors, influences the general practitioner to prescribe a blood pressure and/or lipid-lowering drug.

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CHAPTER 3

The effect of screening for cardio-renal risk factors on drug use in the general population

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Submitted

ABSTRACT

Introduction

A screening procedure is aimed to select people at high-risk for an unfavorable health outcome for further investigation and treatment. It however, might increase medical consumption and drug use. The aim of this study is to evaluate the effect of a cardiovascular and renal screening program on desired-, and on undue drug use. We will evaluate the impact of screening of an aselect, but also of a targeted cohort, that is a cohort enriched for the presence of cardiovascular and renal risk factors.

Methods

We used data from PREVEND (Prevention of REnal and Vascular ENd-stage Disease) cohort study. For this analysis, the drug use of a random sample of screened subjects (the aselect cohort, *n*=2650) is compared with drug use in subjects not participating in the screening program, matched on age and sex (the unscreened reference group, *n*=10,434). The drug use in the overall PREVEND cohort, that was enriched for the presence of an elevated albuminuria (enriched cohort , *n*=6751), was also studied. The main outcome was incidence of drug use following the screening. We selected screening-related drugs e.g. antihypertensive, antilipidemic, antidiabetic and antithrombotic agents, as well as screening-unrelated drugs e.g. benzodiazepines, drugs for acid related disorders, and pain killers. Time to first prescription after screening is presented as Kaplan Meier curves.

Results

After 6.5 years of follow up the cumulative incidence of drug use was not significantly different between the screened aselect and the unscreened cohort. Antihypertensives were used by 21.5 and 20.8% of the screened and unscreened subjects, respectively, antilipidemic drugs by 12,8 and 10.2%, antidiabetics by 4.0 and 3.9%, and antithrombotic drugs by 11.4 and 12.0%. Screening-unrelated drugs were also used in comparable frequencies. As compared to the unscreened cohort screening related drugs had been prescribed more frequently to the subjects of the enriched PREVEND cohort (25.8, 15.5, 5.5, and 13.5% for the antihypertensive, antilipidemic, antidiabetic and antithrombotic drugs, respectively), while screening unrelated drugs were used in comparable frequencies.

Conclusions.

The incidence of drug use is not different in a screened aselect cohort as compared to an unscreened cohort. Our data thus show that screening does not lead to more drug prescriptions, and thus argues against the fear of undue medicalisation after a screening. The data also show that, for a screening to be successful, it should be performed in a targeted population, such as for example in a population enriched for having elevated albuminuria.

INTRODUCTION

A population screening is meant to detect people at risk of an unfavorable health outcome for further investigation and subsequent advice and treatment. The most important benefit from detecting disease at an earlier stage is that treatment can be started earlier and may therefore be more effective. Screening and treatment of cardiovascular and renal risk factors such as hypertension, diabetes, hyperlipidemia and proteinuria can reduce the incidence and progression of cardiovascular and renal disease [1-5].

Whereas only a small proportion of the people screened will benefit from the screening program, some participants may also experience harm [6-7]. It is for example known that participants may experience psychological distress, including anxiety provoked by the screening procedure itself, the time waiting for the result and treatment of the disease for which is screened [7-10]. It has also been argued that screening may result in medicalisation [6,11-12] and thus may lead to increased drug use [13-15]. Indeed, hypertension and vascular disease screening programs have been found to result in an increased use of antihypertensive and lipid lowering drugs [16-17] . This may be undue use of these agents in asymptomatic patients and may also relate to an excessive use of drugs in general. The studies done thus far, however, did not compare the use of cardio- and renoprotective drugs in the screened population with the use in the unscreened population. These studies also did not test whether the awareness of being at risk for cardiovascular and renal disease may already result in an increased use of other drugs, not directly related to the diseases tested for.

We therefore evaluated in this study the effect of screening for cardiovascular and renal risk factors on drug use in a screened population as compared with a non-screened reference population. We looked for the use of drug groups that are related to the purpose of the screening, as well as for the use of drugs unrelated to the screening purpose. We similarly evaluated the drug use in a cohort that is enriched for the presence of cardiovascular and renal risk factors.

METHODS

Design

For this study we used data from the PREVEND screening program (Prevention of REnal and Vascular ENd-stage Disease), running in the city of Groningen, the Netherlands. In this report we studied drug use in a random sample of 3432 subjects of the Groningen population in the age of 28-75 years [18] for description of the cohort). Drug use in this *screened aselect cohort* was compared with the drug use in the background *unscreened population* of the same age and city (Figure-1). Drug use of both the PREVEND participants and the background population was monitored from the InterAction DataBase (IADB), which contains pharmacy-dispensing data of a population of approximately 500,000 subjects in the Northern part of the Netherlands. This database contains, among other things, the name of the drug, the date the drugs were prescribed and their ATC (Anatomical Therapeutical Chemical) code. The use of over-the-counter drugs and in-patient prescriptions is not included [19] .

As the PREVEND study is designed to investigate the impact of urinary albumin excretion on renal and cardiovascular disease progression in the general population, the overall PREVEND cohort of 8592 subjects is enriched for the presence of an elevated albuminuria (*the screened enriched cohort)*. Design and methods of the PREVEND study have been described in detail elsewhere [20,21]. In the present analysis subjects with available drug information from the pharmacy prescription database at least 6 months prior to the screening were included. Of the 3432 subjects of the screened aselect cohort 2650 were eligible for analysis, and of the 8592 subjects of the enriched cohort 6751 were eligible. The screened subjects were seen for a second screening after a median follow up of 4.2 years. After both screenings the subjects and their general physicians were informed in case of hypertension (>160/100 in 1997/98 and, dependent on age and cardiovascular risk, >140/90 in 2001/2), and hyperlipidemia (>8.0 or >5.0 in case of a previous myocardial infarction) to contact their general practitioner, as it was advisable to start blood pressure lowering or lipid lowering treatment [22] . After the first screening 3.0%, and 3.9% of the subjects in the screened aselect cohort received a letter to consider the start of blood pressure- or lipid-lowering drugs, respectively. After the second screening these percentages were 6.0% and 4.3%, respectively. We did not advice on the use of antithrombotic drugs. In the screened enriched cohort 5.5 and 4.6 of the subjects received a letter to start blood pressure- or lipid-lowering treatment respectively, after the first screening, and 6.7 and 5.3 after the second screening.

As reference group we used data of 181,993 subjects aged between 28 and 75 years old at July 1st 1998, living in the city of Groningen, and not participating in the PREVEND screening program, and of which pharmacy data were available from at least 6 months before July 1st 1998 (hypothetical screening date). We randomly selected 10,600 subjects of this cohort matched on age and sex of the PREVEND random sample of 2650 available subjects. Of these subjects, we excluded those who were on insulin prior to screening (as was done for inclusion in the PREVEND study) [20-21] . Thus, 10,434 subjects in the unscreened reference-group are available for analysis. We studied the drug use for at least 180 days before the screening date until 31st of December 2004, thus allowing an approximately 6.5 years of follow-up.

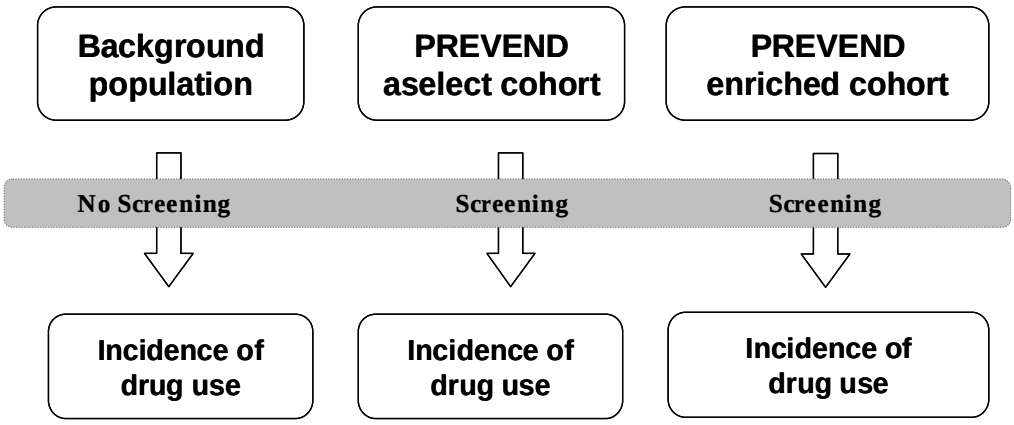


Figure 1. *Flow chart of the study design*

The drugs studied

The drugs studied are categorised according to World Health Organisation following of the Anatomical Therapeutic Chemical (ATC) classification system [23]. The study evaluated two major drug groups. First, the screening-related drugs (drugs prescribed to improve cardiovascular and renal outcome). This group consists of blood pressure lowering drugs, including diuretics (ATC code C03) beta blockers (C07), calcium channel blockers (C08) and drugs interfering in the renin angiotensin system (C09), lipid lowering drugs (C10), blood glucose lowering drug (A10B for prevalence and A10 for incidence) and antithrombotic drugs (B01). The second group studied are screening-unrelated drugs, e.g. drugs of which the screening is not intended to influence its use. To that purpose we evaluated use of benzodiazepine and antidepressants (N05BA, N05CD, N05CF, N06A, and N06CA), H-2 receptor antagonists and proton pump inhibitors (A02BA and A02BC), and

pain killers (M01, M03B and N02). We choose for these drug classes as stress (due to the awareness of being at risk) might result in more frequent use of these agents.

Statistical analysis

Analyses were performed using SPSS version 13.0 software (SPSS, Chicago, IL, USA). The proportion of the subjects who had received at least one prescription in the 6 months before screening is presented as prevalent drug use at screening. The proportion of the subjects who started to use a drug following the screening is presented as the cumulative incidence. The incidence figures include the subjects who did not use a selected drug 180 days before the screening. The cumulative incidence is presented by Kaplan-Meier survival estimation from the screening date until 6.5 years of follow-up. Subjects who moved out of the city of Groningen were censored. The proportional hazard ratio with 95% confidence intervals is used to calculate the difference between index and reference group.

RESULTS

Prevalence of drug use prior to the screening

Of the 2650 subjects in the screened aselect cohort and the 10,434 subjects in the unscreened cohort (reference group), 42% were male and mean age on the first screening date was 49.4 years. Of the 6751 subjects in the enriched cohort 47.3% were male and mean age was 50.0 years.

Table-1 shows the prevalent use of studied drug groups in the 6 months prior to the baseline screening. The prevalent use of screening related drugs was not significantly different between the screened aselect cohort (19.1%, 95% CI 17.6-20.6) and the unscreened cohort (20.6%; 19.8-21.4, p=0.09). In the subgroups, the prevalent use of blood pressure lowering and lipid lowering drugs before the screening was not significantly different between the screened aselect cohort and the unscreened cohort PREVEND (15.3% *vs* 16.5% and 4.9% *vs* 4.9%, respectively). In contrast, the use of blood glucose lowering and antithrombotic drugs was significantly lower in the screened aselect cohort (1.2% and 5.1% resp.) than in the unscreened group (2.2% and 7.3%, resp.). In the screened enriched cohort the use of screening related drugs was higher (22.2%; 21.2-23.2) than in the unscreened cohort (p=0.01). This was due to a greater use of especially blood pressure- and blood glucose- lowering drugs.

Table-1. Use of selected drugs in the 6 months prior to the baseline screening

Selected drugs	Unscreened Cohort n = 10,434	Screened aselect cohort n = 2650	p-value†	Screened enriched cohort n = 6751	p-value ‡
Screening-related drugs (%)	2149 (20.6)	506 (19.1)	0.09	1500 (22.2)	0.01
1. Blood pressure lowering drugs (BPLD)	1721 (16.5)	406 (15.3)	0.14	1211 (17.9)	0.01
2. Lipid lowering drugs (LLD)	509 (4.9)	131 (4.9)	0.89	359 (5.3)	0.06
3. Oral blood glucose lowering drugs (BGLD)	232 (2.2)	32 (1.2)	0.001	113 (1.7)	0.01
4. Anti thrombotic drugs (ATD)	765 (7.3)	136 (5.1)	<0.001	479 (7.1)	0.56
Screening-unrelated drugs (%)	3676 (35.2)	849 (32.0)	0.02	2203 (32.6)	<0.001
1. Benzodiazepines and antidepresssants	1909 (18.3)	395 (14.9)	<0.001	1027 (15.2)	<0.001
2. H-2 receptor antagonist and proton-pump inhibitors	755 (7.2)	191 (7.2)	0.96	498 (7.4)	0.73
3. Painkillers	2236 (21.4)	544 (20.5)	0.31	1381 (20.5)	0.13

p-value † indicates whether drug use differs between screened aselect cohort and unscreened cohort as reference, using chi-square test; p-value ‡ indicates whether drug use differs between screened enriched cohort and unscreened cohort as reference, using chi-square test;

The use of screening-unrelated drugs before the screening was significantly lower in the screened aselect (32.0%; 30.3-33.8) and the screened enriched cohort (32.6%; 31.5-33.8) as compared to the unscreened reference group (35.2%; 34.1-36.4; $p<0.05$). When studying the various drug subgroups, prevalent use was significantly lower in both screened cohorts for benzodiazepines and antidepressants (14.9% and 15.2% *vs* 18.3%, both $p<0.001$), while the use of H-2 receptor antagonist and proton pump inhibitors, and also painkillers was not significantly different between the two screened cohorts and the unscreened reference group.

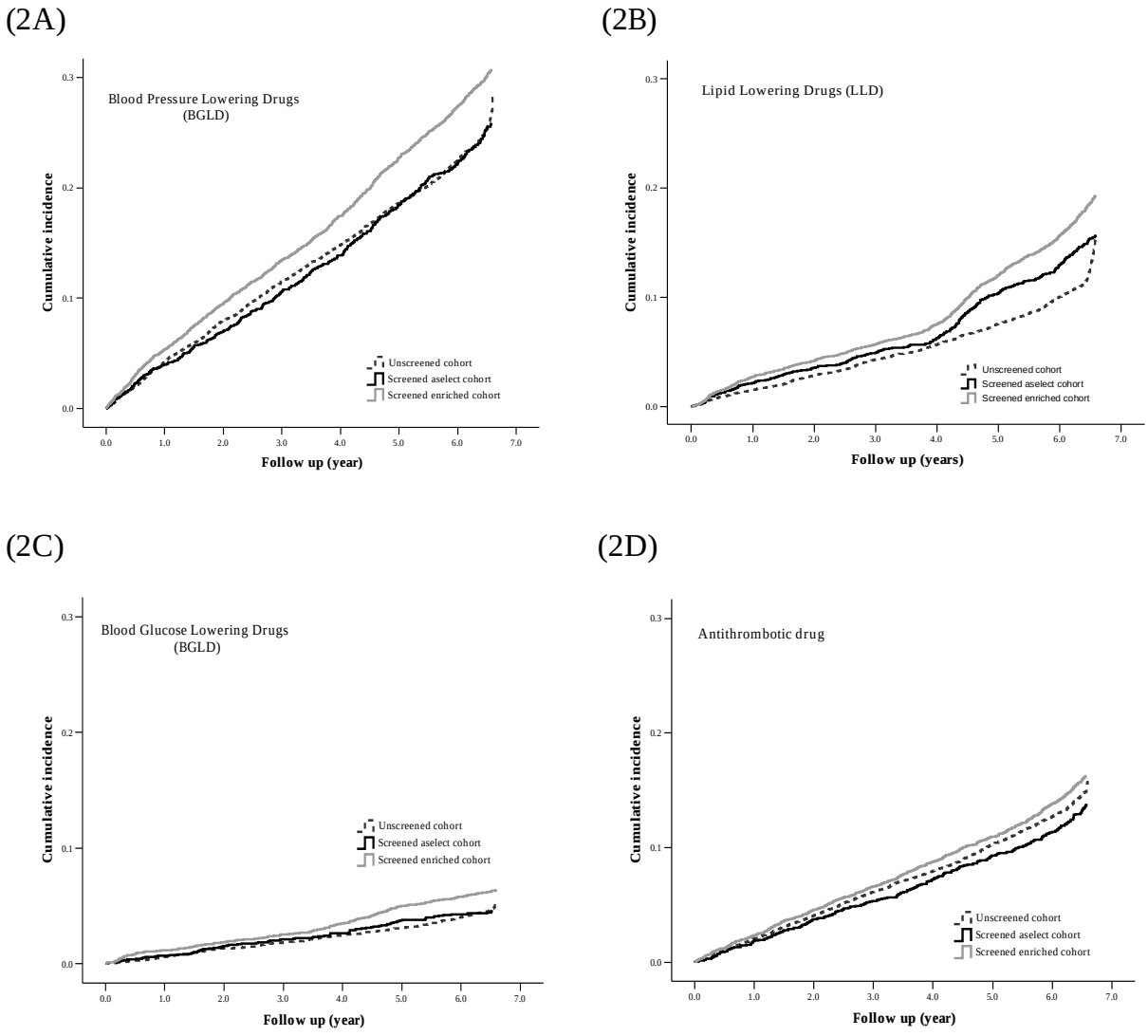


Figure-2. *Cumulative incidence of use of screening-related drugs, e.g. blood pressure lowering drugs (2A), lipid lowering drugs (2B), oral blood glucose lowering drugs (2C) and anti-thrombotic drugs (2D) in the screened aselect cohort (continuous dark-line), the screened enriched cohort (continuous gray-line) and the unscreened reference cohort (broken line).*

Table-2. Cumulative incident use of selected drugs at 6.5 years after the baseline screening

Selected drugs	Unscreened cohort	Screened aselect cohort	HR (95% CI) †	Screened enriched cohort	HR (95% CI) ‡
Screening-related drugs (%)	26.0	27.9	1.02 (0.94-1.12)	32.2	1.20 (1.13-1.29)
1. Blood pressure lowering drugs (BPLD)	20.8	21.5	0.98 (0.88-1.08)	25.8	1.18 (1.10-1.27)
2. Lipid lowering drugs (LLD)	10.2	12.8	1.20 (1.05-1.36)	15.5	1.39 (1.27-1.52)
3. Oral blood glucose lowering drugs (BGLD)	3.9	4.0	0.99 (0.79-1.23)	5.5	1.28 (1.11-1.48)
4. Anti thrombotic drugs (ATD)	12.0	11.4	0.89 (0.78-1.02)	13.5	0.99 (0.90-1.08)
Screening-unrelated drugs (%)	70.4	72.0	1.04 (0.97-1.10)	71.9	1.04 (0.99-1.09)
1. Benzodiazepines and antidepresssants	35.9	36.2	0.98 (0.90-1.06)	35.9	0.98 (0.93-1.04)
2. H-2 receptor antagonist and proton-pump inhibitors	31.7	27.3	0.83 (0.72-0.95)	27.6	0.86 (0.78-0.95)
3. Painkillers	60.7	64.7	1.07 (1.01-1.14)	64.2	1.07 (1.03-1.12)

† Hazard Ratio (HR) of drug use at 6.5 years after the baseline screening, between screened aselect cohort and unscreened cohort as reference group, matched for sex and age, using Cox-regression analysis.; ‡ Hazard Ratio (HR) of drug use at 6.5 years after the baseline screening, between screened enriched cohort and unscreened cohort as reference group, adjusted by sex and baseline age, using Cox-regression analysis.

The incidence of drug use in the screened aselect cohort

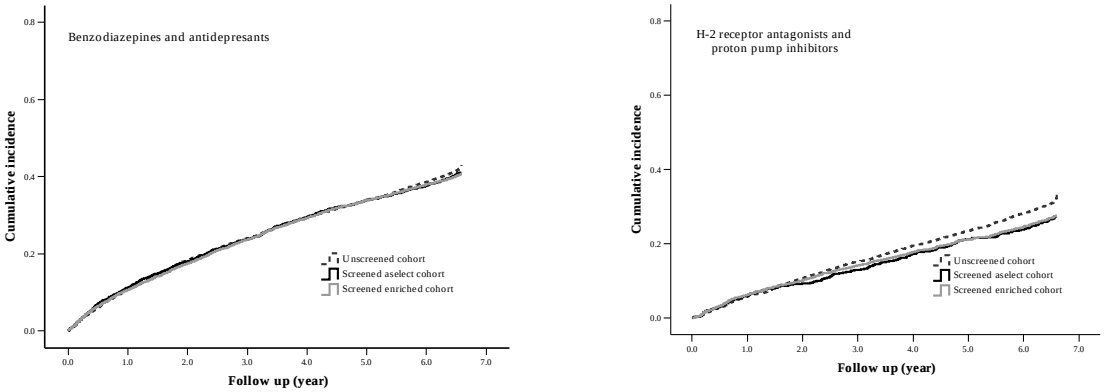
At the end of the follow up there was no difference in the cumulative overall incidence of drug use between the screened aselect cohort and the unscreened reference cohort, neither for the screening-related drugs (27.9 *vs* 26.0%; HR 1.02, 95% CI 0.94-1.12) nor for the screening-unrelated drugs (72.0 *vs* 70.4%; HR 1.04, 0.97-1.10). If anything, the use of non screening-related drugs was lower in the screened aselect cohort (Table-2).

The cumulative incidences of blood pressure lowering, blood glucose lowering and antithrombotic drugs were not different between the screened aselect and the unscreened cohort. The cumulative incidence of new drug use at the end of the 6.5 year follow up amounted to 21.5 and 20.8% for blood pressure lowering drugs (Figure-2a), 4.0 and 3.9% for blood glucose lowering drugs (Figure-2c) and 11.4 and 12.0% for the antithrombotic drugs (Figure-2d), in the screened aselect cohort and the reference group, respectively. The incidence of the use of lipid lowering drugs however, was higher in the screened aselect cohort compared to the reference group (HR 1.20; 95% CI 1.05-1.36) (Figure-2b). This seems to be manifest especially in the first year and after about 4 years of follow up, e.g. at the time of both screenings. When looking at the various subgroups of screening-unrelated drugs, the subjects in the screened aselect cohort started the use of benzodiazepines and anti-depressants, H2 receptor antagonists and proton pump inhibitors, and painkillers at a comparable frequency as in the background population (Figure-3 a-c).

The incidence of drug use in the screened enriched cohort

At the end of the follow up the cumulative incidence of use of screening related drugs was greater in the screened enriched cohort compared to the unscreened cohort (32.2 *vs* 26.0%; HR 1.20, 1.13-1.29), while the use of screening unrelated drugs was not different between both groups (71.9 *vs* 70.4%; HR 1.04, 0.99-1.09) (Table-2). The higher incidence of use of screening related drugs was manifest for the three drug groups on which we gave therapeutic advice (blood pressure-, lipid- and blood glucose-lowering drugs), but not for the other cardioprotective agents for which we did not give specific advice, e.g. antithrombotic drugs (Table-2 and Figure-3). When looking at the various subgroups of screening unrelated drug groups, the use of benzodiazepine and antidepressant was not different between the screened enriched cohort and the unscreened cohort, while drugs for acid related disorders were used less frequently in the screened cohort and painkillers were used more frequently.

(3A) (3B)



(3C)

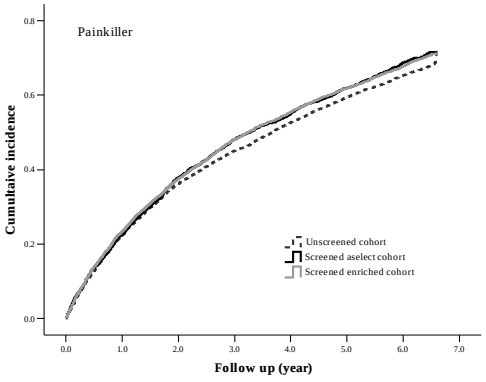


Figure-3. Cumulative incidence of use of screening-unrelated drugs, e.g. benzodiazepines and anti-depressants (3A), H2 receptor antagonists and proton pump inhibitors (3B), and painkillers (3C) in the screened aselect cohort (continuous dark-line), the screened enriched cohort (continuous gray-line) and the unscreened reference cohort (broken line).

DISCUSSION.

Our data show that screening for hypertension, diabetes and hyperlipidemia does not result in a higher drug use in a screened aselect sample of the population as compared to the background non-screened population. Screening neither influenced the incidence of the use of drugs which are related to the rationale of the screening program, nor for screening unrelated drugs. Only the use of lipid lowering drugs was higher, especially shortly after the first and second screening.

At first sight, we were impressed by the finding that in a screening amongst the general population in the age range of 28-75 years 21.5% of the subjects that were not yet on antihypertensives at the time of the screening started to use those drugs in a period of 6.5 years and 12.8% and 11.4% started lipid

lowering and antithrombotic treatment, respectively. These figures suggest a clear medicalisation of the screened population. We however found nearly identical figures on incident drug use in the unscreened reference group. This emphasizes that screening per se does not lead to medicalisation, but that cardio- and renoprotective drug use in the general population is growing rapidly. That data are in agreement with other studies that showed a growing use of both antihypertensives [24-25] and lipid lowering drugs [25-27]. This growth has been argued to be related to both pharmaceutical marketing and publication [28-30] and better implementation of, and adherence to, guidelines [31].

The data on incident use of lipid lowering drugs show the impact of the screening procedure itself. Both after the baseline screening (year 0.0), as well as after the second screening (year 4.2) the two curves dissociate, the screened aselect cohort using lipid lowering drugs more frequently. This, at least partly may be related to the fact that 4.0% and 4.3% of the screened subjects were sent a letter after the first and second screening, respectively, to start such treatment. After a given time period however, this difference disappears. Notice that the discrepancy is more pronounced after the second screening. In those years (2001/02) prescribing lipid lowering drugs was widely advocated in guidelines in our country. As a consequence the use of these agents increases not only in the screened aselect cohort , but also in the unscreened population.

We could also interpret our data as a failure of screening programs to optimise drug treatment by starting treatment in an earlier, still asymptomatic phase. Our data on drug use in the screened enriched cohort, e.g the group of subjects enriched for the presence of albuminuria, nicely show that screening for risk factors should be carried out in a targeted population. Only then subjects with risk factors are selected from the population and screening may thus become cost-effective [22]. A pre-screening on albuminuria may be an adequate approach to reach that goal [18,34]. The impact of the information to the participant that specific treatment should be started is clear from the difference in incident drug use between the aselect and enriched cohort. That the treatment is limited only to the categories adviced is also clear from the finding that the use of antithrombotic drugs (on which we did not advice) was not higher in the enriched cohort.

At baseline, for some drug groups the use was lower in the screened aselect sample than in the non-participants. This was the case for oral blood glucose lowering drugs and antithrombotic drugs, for the group of screening unrelated drugs in general, and benzodiazepines and antidepressants in particular. It illustrates that participants in a screening are in general healthier than non-participants. The lower prevalence of oral blood glucose lowering drugs in the

screened population may be due to the fact that insulin using diabetics were not included in our screening program (as PREVEND wants to evaluate the impact of albuminuria in the general population instead of in the diabetic population). This may well explain the fact that subjects participating in the screening were also less frequently using antithrombotic drugs. Our finding of a higher use of psychotrophic medication in non-participants to the screening is in line with data from the Tromso Health Study. In that study patients with psychiatric disorders had an approximately 20% lower attendance rate to the health survey, and non-participants to the survey had a 2.5 times higher prevalence of psychiatric disorders than did participants [33] .

Our study has some shortcomings. First, we measured drug use from a pharmacy database. That means that the drugs reported have been delivered to the patient. We however, are not informed on the actual drug use by the patient. Second, we are not aware whether the patients used blood pressure lowering drugs indeed as antihypertensive or for another indication, such as beta blocking drugs for angina or ACE inhibitors for heart failure. This uncertainty regarding the diagnosis is less likely a problem for the other drug categories. Third, drug use is just one of the components of medicalisation. We for example are not aware on medical consumption in general, such as frequency of physician-contacts, medical diagnostic procedures or life style changes.

It is a strength of our study that we were able to compare drug use in a screened cohort with that in a large cohort in the same city, matched for sex and age. Second, we could provide data on a long period of follow-up (6,5 years). Third, drug prescription data have been validated to be a reliable form of information on drug use and have the advantage over patient histories, that the latter are hampered by recall bias [34]. Moreover, in the Netherlands most of the drugs are delivered on prescription via the pharmacies, and a patient receives nearly always all drugs from the same pharmacy.

In conclusion, our data show that a screening program to improve cardiovascular and renal outcome does not lead to a higher drug use than in an unscreened population. The data also show that a targeted screening, that is a screening in a cohort that likely is at higher risk, contributes to a greater drug use, but only in the drug classes expected and not in an overall undue drug use.

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CHAPTER 4

The effect of statins on urinary albumin excretion and glomerular filtration rate: results from both a randomized clinical trial and an observational cohort study

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ABSTRACT

Introduction

Statins improve cardiovascular outcome, but less is known on renal outcome. We therefore studied the relation between statins use and urinary albumin excretion (UAE) and GFR in two settings: an RCT and an observational cohort study, in which patients were included to study the impact of an elevated UAE on renal and cardiovascular prognosis.

Methods

We used data from the PREVEND-IT and the PREVEND cohort study. The PREVEND-IT subjects (788 with a UAE 15-300 mg/day) received pravastatin 40 mg/day vs placebo and/or fosinopril 20 mg/day vs placebo in a 2x2 factorial-RCT design. Of the cohort subjects (3440) 469 used statins during the 4-year follow-up period. Multivariate regression adjusted for confounding factors and propensity score was used to estimate the relation between statin use and UAE and GFR.

Results

In the RCT, pravastatin did not change UAE or GFR, neither in the fosinopril yes/no sub-groups. In the observational cohort statin use was associated with a rise in UAE (+12.1%), compared with non-users (+3.6%, $p<0.001$). This rise was most pronounced in those on statins prior to screening-1 (+24.8% [95% CI: 11.9-39.2]), those using statins >3 years (+18.5% [7.3-30.8]) and those with >1 or >2 defined daily doses (+15.7 and +17.3%, resp). These differences remained significant after adjustment for relevant variables and propensity score. The rise in UAE could not be attributed to a higher dose or a specific statin. GFR fell in 4 years in both statin users and non-users (4.6±13.5 and 2.4±11.2, resp). The fall in GFR between groups was not different after adjustment ($p=0.11$).

Conclusions

We conclude from the RCT data that statins do not lower UAE in subjects selected because of an elevated UAE instead of hyperlipidemia. In the observational cohort study the use of statins similarly was not associated with a fall in UAE, UAE instead increased. Statin treatment was not associated with a significant change in GFR in these subjects with only modestly impaired GFR.

INTRODUCTION

Statins (HMG-CoA reductase inhibitor) are widely used for lowering of LDL and total cholesterol. It has been well documented that these drugs improve cardiovascular outcomes [1-5]. Less is known on the effect of statins on renal outcome, e.g. on urinary albumin excretion (UAE) and glomerular filtration rate (GFR). Experimental studies showed statins to have a renoprotective effect [6,7]. Human data mostly report a statin induced lowering of UAE in patients with advanced renal disease [8] and in type 2 diabetic patients with microalbuminuria [9-11], but no change [12] or even an increase in albuminuria has also been described [13-16].

With respect to the preservation of renal function, recent analyses of some large cardiovascular trials suggested renal function to benefit from statin therapy [17-21]. These are secondary or post hoc analyses of kidney function in studies in large secondary prevention trials mostly performed in high risk individuals with high cholesterol levels. The impact of statins in subjects with an elevated UAE without clearly elevated cholesterol levels has not been studied yet. To that purpose we analyzed the effects of statins on UAE and GFR in a clinical trial that was performed in subjects with a urinary albumin loss of 15-300 mg/day (the PREVEND-IT study). As data derived from a randomized controlled trial (RCT) cannot be extrapolated to daily clinical practice [22], we in addition studied the relation between statin use and UAE and GFR in an observational cohort study (the PREVEND study).

METHODS

Study design and population

This study is part of the PREVEND (Prevention of Renal and Vascular End-stage Disease) study, an ongoing, prospective study which is designed to investigate the impact of urinary albumin excretion on renal and cardiovascular disease in the general population. The formation of the study cohort has previously been described in detail [23]. Briefly, in 1997 a cohort of subjects aged 28-75 years enriched for an elevated urinary albumin excretion was drawn from the population of the city of Groningen. Overall 8592 subjects gave written informed consent and were included in 1997 in the observational cohort for extensive baseline screening. Of these 8592 subjects, 864 were selected for the PREVEND Intervention Trial (PREVEND IT), a clinical trial aimed to study the effect of

fosinopril and pravasatin on cardiovascular outcome (see below). The local medical ethics committee approved the PREVEND and the PREVEND-IT studies.

The observational cohort study

These 8592 subjects were followed for cardiovascular and renal morbidity and mortality since baseline screening. They were invited for a 2nd screening after a mean follow-up of 4.2 years (range 2.8-6.1). By then 246 subjects had died, 130 were lost to follow up and 1322 declined participation, leaving 6894 subjects who completed the second screening. Of these 6894 subjects we excluded those who participated in the PREVEND IT study (*n*=758), those of whom no complete information on drug use was available from the pharmacy prescription database (IADB) (*n*=2632) (see below), and the 64 subjects with incomplete data for the requested clinical parameters. Subjects with missing data were not different from the included subjects with respect to baseline characteristics. Thus 3440 subjects are available for analysis: 2963 who during the study period never had used statins and 477 statin users. The changes in UAE and in GFR from baseline versus second screening were studied in relation to the use of statins. The number of subjects included in this follow up allowed us to detect a difference in change in UAE of at least 0.20 mg/d and a change in GFR of at least 0.79 ml/min between statin users and non-statin users over the 4.2 year observational period with 80% power and alfa 0.05.

The PREVEND Intervention Trial (clinical trial)

The protocol of this study and the results on cardiovascular outcome have been described in detail elsewhere [23]. In short, 864 of the 8592 subjects participating in the PREVEND follow up cohort were included in this clinical trial. They were included when they had a UAE of 15-300 mg/day, a blood pressure less than 160/100 mmHg without use of antihypertensives, and plasma cholesterol <8.0 mmol/L, or <5.0 mmol/L in case of a previous myocardial infarction and without the use of lipid lowering agents. These 864 subjects were treated in a double blind, randomised, placebo-controlled trial with a 2x2 factorial design with fosinopril 20 mg/day or matching placebo and with pravastatin 40 mg or matching placebo during four years. In the present analysis the 788 subjects were included, of whom follow up on treatment was complete (*n*=644) or follow up of at least 3 months on treatment (the time that UAE and GFR were first measured on treatment) was available (*n*=144). The other 63 subjects had withdrawn from treatment before the effects of statin or placebo on UAE and GFR could be measured and 13 subjects had incomplete data for the requested clinical parameters. The changes in UAE

and GFR from baseline (that is for the start of the trial drugs) versus 4 year of follow up are used. The number of subjects without use of fosinopril (*n*=392) included in this study allowed us to detect a difference in change in UAE of at least 0.54 mg/d and a change in GFR of at least 2.16 ml/min between paravastatin and placebo over the 4 year observation period, with 80% power and alfa 0.05.

In those subjects that stopped the statin or matching placebo before the end of the trial study period, the last available value of UAE and GFR on treatment is used (last-value-carried-forward analysis).

Measurements in both study protocols

The methodology used in both the PREVEND observational cohort and for the PREVEND–IT randomised controlled trial has been described previously [23-24]. The screening examination included an interview on demographics, medical history and smoking habits. During physical examination, weight, height and blood pressure were measured. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). Systolic and diastolic blood pressure were measured on two separate occasions in supine position at the right arm every minute for ten minutes with an automatic Dinamap XL Model 9300 series monitor (Johnson-Johnson Medical Inc, Tampa, Florida). Blood pressure was calculated as the mean of the last two measurements at both visits. Fasting blood was drawn for determination of total cholesterol, glucose and serum creatinine. Furthermore urine was collected during two days for measurement of urinary albumin excretion (UAE).

Plasma total cholesterol, plasma glucose and serum creatinine were determined by Kodak Ectachem dry chemistry (Eastman Kodak, Rochester, NY, USA), an automatic enzymatic method. During follow-up serum creatinine was measured by photometric determination with Jaffe method without deproteinisation (Merck KGaA, Darmstadt, Germany). Serum creatinine values at second screening were adjusted using an internally validated correction factor to correct for the change in determination technique. Urinary albumin concentration was determined by nephelometry with a threshold of 1.8 to 2.3 mg/l and intra- and interassay coefficients of variation of less than 2.2% and 2.6% respectively (Dade Behring Diagnostic, Marburg, Germany). Urinary albumin excretion is given as the mean of the two 24-hour urine excretions. GFR was estimated using the Modification of Diet in Renal Disease (MDRD) formula: $186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$.

The prescription database used in the observational study

Information on drug use was obtained from the InterAction Database (IADB), containing pharmacy-dispensing data from community pharmacies in the city of Groningen. Dutch patients usually register at a single community pharmacy and therefore this pharmacy can provide an almost complete listing of subject's prescribed drugs [25]. Pharmacy data contain, among others, information on the name of the drug dispensed, ATC (Anatomical Therapeutical Chemical) classification, date of prescription, number of days the drug was prescribed and the number of defined daily doses (DDDs) based on definition of WHO [26]. The use of over the counter (OTC) drugs and in-hospital prescriptions are not included. Information on drug use was collected from at least one year prior to the date of the first screening until at least the second screening.

Exposure and outcome definitions

Subjects were defined as statin user in case they received at least one prescription of any statin the year preceding the second screening. If they already received a statin in the year prior to the first screening, they were defined as 'continuers'. In case they started using statins after the first screening they were defined as 'starters'. Subjects were considered as 'non statin users', when they had never received a prescription for any statin in the whole study period. We similarly registered the use of antihypertensive medication with a split up in agents interfering in the renin angiotensin system (RAS), such as ACE inhibitors or angiotensin II receptor blockers, and other antihypertensives. Also the use of lipid-lowering and glucose-lowering drugs was registered.

We studied also subgroups of statin users based on the prescribed daily dose (PDD), cumulative time exposure and type of statin. The PDD was calculated from the total amount of DDDs divided by the number of days of exposure. The DDDs for the most frequently prescribed statins in this study are: simvastatin 15 mg, pravastatin 20 mg, and atorvastatin 10mg. PDD was divided into PDD < 1.00, between 1.00-2.00 and more than > 2.00. Cumulative time exposure was divided into use of statin ≤ 1 year, between 1-3 years, and more than 3 years. Subjects who received only one type of statin during the study period were included into the analyses for the type of statin. Subjects who switched from one statin to another or subjects who had used a statin that was prescribed only to a small number of subjects were excluded for subgroup analysis for type of statin.

In both studies we assessed the change in UAE and GFR from first versus second screening as continuous variable. We also assessed a rise in UAE and a fall in GFR as a categorical variable. Subjects were divided into 4 classes of UAE

according to the level of UAE; normo-albuminuria (0-14.9 mg albumin/day), borderline micro-albuminuria (15-29.9 mg albumin/day), micro-albuminuria (30-299.9 mg albumin/day) or macro-albuminuria (> 300 mg albumin/day). Progression was defined as an increase of UAE of at least 50% and a change of at least one class during follow up. A fall in GFR in the categorical analysis was defined as a decline in GFR of at least 10%.

Propensity score

To control for potential differences in the characteristics of subjects between index group (statin users) and reference group (non-statin users), we used propensity scores. Propensity score is the probability that an individual would have been treated with statin based on individual's observed pretreatment (in first screening) variables. The propensity score for an individual can be used to balance the covariates in observational studies, and thus reduce bias. The estimated propensity score for statin treatment was obtained from the fit of a logistic regression model for which we considered the following variables: age, gender, history of myocardial infarction, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, serum cholesterol level, blood glucose level, UAE (in class category), e-GFR, use of antihypertensive, RAS agent and antidiabetic medications.

Statistical analyses

The baseline characteristics in both studies are reported as mean and standard deviation for continuous variables and as percentage for categorical variables. Because of its skewed distribution, logarithmic transformation of UAE was applied for further analyses and reported values are transformed back to the original scale (geometric means). Differences in population characteristics at baseline in the various groups under investigation were tested for continuous variables by Student's t-test and for categorical variables by a Chi-square test.

In our observational study, in the primary analyses we compared the percentage change in log transformed UAE between the first and second screening for each category of statin-user with Student's t-test.

Table-1. Baseline characteristics of the study cohort according to use of statins

	Observational study = 3440		**Randomized controlled trial = 788**	
	No use of statins (n=2963)*	**Use of statins (n=477)***	**Placebo (n=388)****	**Pravastatin (n=400)****
Male (%)	41.3	58.5	62.4	68.8
Age (years)	49.3 (+/- 11.8)	57.9 (+/- 9.8)	50.9 (+/- 11.5)	52.1 (+/- 11.9)
Body mass index (kg/m^2)	26.0 (+/- 4.1)	27.7 (+/- 4.1)	26.2 (+/-4.3)	26.3 (+/- 4.4)
Systolic blood pressure (mmHg)	127.6 (+/- 20.2)	138.5 (+/- 22.1)	130.2 (+/- 16.9)	130.8 (+/- 18.1)
Diastolic blood pressure (mmHg)	73.5 (+/- 9.8)	77.4 (+/- 9.2)	76.0 (+/- 9.7)	76.5 (+/- 9.6)
Glucose (mmol/l)	4.8 (+/- 1.1)	5.5 (+/- 2.2)	4.9 (+/- 1.0)	5.0 (+/- 1.2)
Cholesterol (mmol/l)	5.5 (+/- 1.2)	6.2 (+/- 1.6)	5.8 (+/- 1.0)	5.8 (+/- 1.0)
Urinary albumin excretion (mg/24hr)	9.9 (4.3-23.1)	16.7 (4.9-56.8)	27.2 (12.5-59.4)	25.8 (11.3-58.6)
e-Glomerular filtration rate (ml/min/1.73m2)	79.6 (+/- 13.8)	75.3 (+/- 14.8)	75.5 (+/- 12.0)	75.7 (+/- 12.1)
Smoking (%)	41.4	45.7	34	32.5
History of myocardial infarction (%)	1.5	19	0.5	0.3
Use of statins (%)	0	43.4	0.6	1.4

Continous variables are presented as mean and standard deviation and categorical variables are presented as percentage; Urinary albumin excretion is presented as geometric mean and 95% CI. * p value <.05 for all variables (except smoking) between use of statins and no use of statins (using Student's t-test for comparing means and Chi-square test for comparing prevalences). ** p value >.05 for all variables between pravastatin vs. placebo (using Student's t-test for comparing means and Chi-square test for comparing prevalences)

One way ANOVA was applied to test for changes in UAE between groups. Multivariate linear regression models were built to adjust for baseline age, sex, blood pressure, cholesterol, glucose, urinary albumin excretion, GFR, body mass index, history of myocardial infarction, use of agents interfering in the RAS, the change in blood pressure between the first and second screening, and for individual propensity score. In addition, in the three subgroup analyses (category of PDD, cumulative time and type of statin) we also adjusted for the two other variables. The same analyses were performed to study the association of statins and changes in GFR.

In the second analyses, we compared the association between statins and the progression of UAE, and categorical changes (more than 10%) in GFR, and calculated univariate and multivariate relative risks (RR's) with adjustment for potential confounders and for individual propensity score [27].

In our clinical trial, we compared the change in log transformed UAE and the percentage change in GFR between pravastatin and placebo using Student's t-test. In addition, we performed an analysis separately in subjects who had received fosinopril and in those who did not. All calculations were performed with SPSS version 12.0.1 software (SPSS, Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the observational study and the clinical trial data

Of the 3440 subjects followed in *the observational study*, 477 (13.9%) used statins and 2963 had never used statins in the study period. The characteristics of these subjects at baseline (1st screening) are reported in Table-1. Compared with the subjects that had never used statins, those who used statins were older and more frequently male, had a higher body mass index, blood pressure, plasma glucose, plasma cholesterol and urinary albumin excretion, and had a lower GFR. Furthermore, the statin users tended to have more co-morbidity, as suggested by a higher prevalence of previous myocardial infarction and more frequent use of antihypertensives in general, but also RAS inhibitors in particular and antidiabetics.

The baseline characteristics of the 788 subjects from *the randomised clinical trial*, that fulfilled the inclusion criteria for the present analysis, are also given in Table-1, according to the use of placebo or pravastatin. A comparison of baseline characteristics did not reveal any statistically

Table-2 Use of pravastatin in relation to urinary albumin excretion in the randomized controlled trial

	N	UAE-1 (mean and 95% CI)	UAE-2 (mean and 95% CI)	p value*	% change (mean and 95% CI)	p value**
All						
Placebo	388	27.2 (12.5-59.4)	24.0 (8.9-64.5)	0.002	- 11.9 (-18.6 / -4.8)	Ref.
Pravastatin	400	25.8 (11.3-58.6)	24.0 (9.1-63.5)	0.07	- 6.9 (-13.8 / 0.5)	0.32
No use of fosinopril						
Placebo	194	26.2 (11.4-60.2)	26.7 (9.9-72.4)	0.71	+ 1.9 (-7.8 / 12.7)	Ref.
Pravastatin	198	23.6 (11.6-51.1)	24.0 (9.9-58.2)	0.78	- 1.5 (-11.4 / 9.5)	0.65
Use of fosinopril						
Placebo	194	28.3 (13.8-58.3)	21.5 (8.2-56.9)	<0.001	- 23.9 (-32.3 / -14.6)	Ref.
Pravastatin	202	28.4 (11.1-66.5)	23.9 (8.3-68.8)	0.03	- 11.9 (-21.1 / -1.7)	0.07
	N	**GFR-1 (mean +/- SD)**	**GFR-2 (mean +/- SD)**	**p value***	**% change (mean +/- SD)**	**p value****
All						
Placebo	388	75.5 (+ / -12.0)	74.5 (+ / -12.2)	0.01	- 0.9 (+ / - 10.9)	Ref.
Pravastatin	400	75.7 (+ / -12.1)	76.3 (+ / -22.4)	0.54	+ 1.0 (+ / - 23.7)	0.17
No use of fosinopril						
Placebo	194	75.9 (+ / -11.6)	75.2 (+ / -11.3)	0.21	- 0.4 (+ / - 10.8)	Ref.
Pravastatin	198	76.2 (+ / -11.3)	78.4 (+ / - 28.6)	0.25	+ 0.8 (+ / - 10.2)	0.28
Use of fosinopril						
Placebo	194	75.1 (+ / -12.3)	73.9 (+ / -13.1)	0.03	- 1.4 (+ / - 11.0)	Ref.
Pravastatin	202	75.2 (+ / -12.8)	74.2 (+ / -13.7)	0.08	- 1.0 (+ / - 10.7)	0.70

UAE-1 (UAE at baseline), **UAE-2 (**UAE after 4 years) and **% change in UAE** are presented as geometric means and 95% CI; **GFR-1 =** GFR at baseline**, GFR-2 =** GFR after 4 years**; p-value*** indicates whether mean UAE or GFR is different between baseline and after 4 years follow-up (using paired sample t-test); **p-value**** indicates whether mean percentage change in UAE or GFR in pravastatin group is different compared to placebo (using two-samples t-test)

significant difference between the placebo and active drug treatment groups. However, as compared to the statin users in the observational study, the statin users in the clinical trial were younger, had a lower systolic blood pressure, less frequent a previous myocardial infarction, and used less other drugs. In contrast, the trial subjects in the placebo group were older and had a higher UAE compared with the non-statin users in the observational study.

Propensity score

The logistic regression model with statin use as dependent variable had an area under the ROC curve of 0.82, thus the model fits well. The mean propensity score of statin users was 0.31 (SD +/- 0.23) compared with 0.11 (SD +/- 0.12) for subjects not receiving statins.

The association between statin use and urinary albumin excretion

The effect of pravastatin on UAE in *the randomised clinical trial* is given in Table-2 (top panel). The impact of pravastatin on UAE can in fact only be correctly studied in the non-fosinopril users, as the ACE inhibitor lowered UAE significantly. In the subjects that did not use the ACE inhibitor, pravastatin did not result in a change in UAE (p=0.78), and the change in UAE on pravastatin was not different from the change in the placebo group (p=0.65). The progression in UAE was also not significant different between pravastatin and placebo group (RR 1.15 95% CI 0.76-1.74), neither in those who did not receive fosinopril (1.09; 0.64-1.88), nor in those who received fosinopril (RR 1.26; 0.66-2.41).

The association between statins and changes in UAE in *the observational cohort study* is shown in Table-3. UAE increased by +12.1% (p=0.002) in statin users compared to +3.6% (p=0.001) in those who never used statins. The rise in UAE in the statin users was significantly greater (p=0.008) than in the non-users, also after adjustment for other differences between the two groups and individual propensity score (p<0.001). When studying the various subgroups of statin users, the rise in UAE seems to be greatest in those who used statins continuously (+24.8%), those using the highest PDD of the statin (+17.3%), those with the longest duration of use (+18.5%), and those using pravastatin (+22.3%). These differences remained statistically significant after adjustment for other variables and propensity scores for continuous use (p<0.001), and longest duration of use (p=0.002), but not anymore for the highest PDD and pravastatin.

Table-3. Use of statins in relation to urinary albumin excretion in the observational cohort study

	N	UAE-1 (mean and 95% CI)	UAE-2 (mean and 95% CI)	p value *	% increased (mean and 95% CI)	p value †	p value ‡	p value ¶
No use of statins	2963	9.9 (4.3-23.1)	10.3 (4.2-25.4)	0.001	3.6 (1.6-5.8)	Ref.	Ref.	Ref.
Use of statins (all) #	477	16.7 (4.9-56.8)	18.7 (4.8-72.3)	0.002	12.1 (4.4--20.4)	0.01	<0.001	0.003
Type of user								
Starter	270	16.6 (4.9-57.1)	17.2 (4.6-66.3)	0.50	3.3 (-5.9-13.3)	<0 .001	0.06	0.28
Continuer	207	16.7 (4.9-56.6)	20.9 (5.4-80.5)	<0.001	24.8 (11.9-39.2)		<0.001	<0.001
PDD								
PDD ≤ 1.00	177	14.8 (4.8-45.9)	15.6 (4.5-54.1)	0.33	5.6 (-5.3-17.7)	0.02	0.75	0.75
PDD 1.00-2.00	218	19.0 (5.2-69.4)	21.9 (5.2-93.0)	0.009	15.7 (3.7-29.1)		0.06	0.06
PDD > 2.00	82	15.3 (4.6-51.1)	18.0 (4.9-65.6)	0.09	17.3 (-2.2-40.7)		0.02	0.10
Cumulative time								
≤ 1 year	68	12.4 (4.8-31.9)	12.9 (4.8-35.0)	0.67	4.3 (-14.1-26.7)	0.01	0.21	0.33
1-3 year	156	15.4 (5.3-44.7)	16.3 (4.8-55.7)	0.36	5.8 (-6.2-19.3)		0.11	0.25
> 3 year	253	19.0 (4.9-74.1)	22.5 (5.1-98.3)	0.001	18.5 (7.3-30.8)		<0.001	0.002
Type of statins								
Simvastatin	197	16.9 (4.8-59.7)	18.2 (4.7-70.0)	0.20	7.6 (-3.8-20.3)	0.06	0.81	0.80
Atorvastatin	121	19.3 (5.0-74.8)	21.8 (4.6-102.4)	0.10	13.1 (-2.0-30.6)		0.90	0.39
Pravastatin	63	13.7 (4.5-41.7)	16.8 (4.9-57.7)	0.04	22.3 (1.8-47.0)		0.21	0.69

UAE-1 (UAE at first screening)**, UAE-2 (**UAE at second screening)**, % change** in UAE are presented as geometric mean and 95% CI; **#** : all subjects who used statins (defined as subjects who had used any statins a year prior to second screening, *see methods section*); **PDD** : prescribed daily dose; **p-value*** indicates whether UAE differs between first and second screening (using paired sample t-test); **p-value†** (crude) indicates whether delta UAE differs between groups (using one way ANOVA); **p-value‡** associated with dummy variable for group, adjusted for baseline age, sex, blood pressure, cholesterol, glucose, UAE, body mass index, history of myocard infarct, start use RAS inhibitors, change on blood pressure, type of statins (for PDD) and PDD (for type of statins) (using multivariate linear regression analysis); **p-value¶** adjusted for all those variables and individual propensity score

The statin users had a higher risk of being progressor in class of UAE compared to non-statin users (16% *vs* 9%; $p<0.001$) with an covariates and propensity score adjusted relative risk of 1.49 (CI 1.07-2.08). In the various subgroups, the risk for being a progressor was significant in continuers (22% *vs* 9%; $RR_{adj.} = 1.71$; CI 1.11-2.62) and in those with the cumulative time 1-3 years (18% *vs* 9%; $RR_{adj.} = 1.70$; CI 1.07-2.82).

The association between statin use and GFR

In *the randomised clinical trial*, in the overall analysis, thus not separated for using an ACE inhibitor or not, the use of placebo was associated with a fall in GFR ($p=0.014$), while GFR did not change in the group that used the statin ($p=0.539$). The difference in continuous changes in GFR on pravastatin compared with placebo was not significantly different in the overall analysis (p=0.165), neither in the sub-groups who used an ACE inhibitor, nor in those who did not (Table-2, bottom panel). Analysed in a categorical way, the fall in GFR was also not significantly different between pravastatin and placebo (RR 0.82 95% CI 0.56-1.19), neither in those who did not receive fosinopril (0.63; 0.36-1.10), nor in those who received fosinopril (RR 1.02; 0.61-1.70).

Table-4 shows the association between statins and continuous changes in GFR in *the observational cohort study*. GFR fell 4.6% (±13.5) in those who used statins ($p<0.001$) as compared to 2.4% (± 11.2) ($p<0.001$) in those who never used a statin. The difference in changes in GFR between these two groups was not statistically different after adjustment for covariables and individual propensity score ($p=0.35$). The fall in GFR, when analysed as 10% change was also not significantly different between the statin users (30,2%) and non- statin users (23,6%) (RR 1.17 95% CI 0.91-1.51). When looking at the various subgroup analyses, neither the continuous nor the categorical fall in GFR was significantly different in those who continued, those with the highest PDD, the longest duration of use, or in any of the individual statins compared to the group who never used statins during the study. The only significant difference observed was a fall in GFR in the group that started use of statins after the first screening.

Table-4. Use of statins in relation to GFR in the observational cohort study

	N	GFR-1 (mean +/- SD)	GFR-2 (mean +/- SD)	p value *	% changed (mean +/- SD)	p value †	p value ‡	p value ¶
No use of statins	2921	79.5 (+/-13.8)	77.3 (+/-13.9)	<0.001	- 2.4 (+/- 11.2)	Ref.	Ref.	Ref.
Use of statins (all) #	469	75.3 (+/-14.6)	71.5 (+/-15.2)	<0.001	- 4.6 (+/- 13.5)	<0.001	0.11	0.35
Type of user								
Starter	266	75.8 (+/-14.4)	71.5 (+/-15.2)	<0.001	- 5.3 (+/- 13.5)	<0.001	<0.01	0.04
Continuer	203	74.6 (+/-14.9)	71.4 (+/-15.3)	<0.001	- 3.7 (+/- 13.5)		0.31	0.37
PDD								
PDD ≤ 1.00	175	74.4 (+/-14.0)	71.3 (+/- 14.0)	<0.001	- 3.3 (+/- 12.5)	<0.001	0.31	0.23
PDD 1.00-2.00	214	75.2 (+/- 14.8)	70.4 (+/- 15.9)	<0.001	- 6.2 (+/- 15.0)		0.73	0.92
PDD > 2.00	80	77.6 (+/- 15.6)	74.8 (+/- 15.7)	0.006	- 3.1 (+/- 11.0)		0.07	0.05
Cumulative time								
≤ 1 year	67	76.8 (+/-14.3)	71.4 (+/-14.7)	<0.001	- 6.5 (+/- 13.4)	0.001	0.06	0.09
1-3 year	154	75.5 (+/-15.2)	72.4 (+/-15.6)	<0.001	- 3.7 (+/- 14.0)		0.79	0.97
> 3 year	248	74.8 (+/-14.4)	71.0 (+/-15.1)	<0.001	- 4.6 (+/- 13.2)		0.21	0.62
Type of statins								
Simvastatin	195	75.1 (+/-15.4)	71.3 (+/- 14.6)	<0.001	- 4.2 (+/- 11.9)	0.001	0.91	0.83
Atorvastatin	118	76.7 (+/- 15.2)	72.1 (+/- 17.4)	<0.001	- 5.9 (+/- 17.0)		0.21	0.24
Pravastatin	63	75.2 (+/- 12.5)	71.5 (+/- 14.5)	0 .002	- 4.8 (+/- 11.4)		0.56	0.66

GFR-1 = GFR at first screening**, GFR-2 =** GFR at second screening**; #** : all subjects who used statins (defined as subjects who had used any statins a year prior to second screening, *see methods section*) **PDD** : prescribed daily dose; **p-value*** indicates whether GFR differs between first and second screening (using paired sample t-test); **p-value†** (crude) indicates whether delta GFR differs between groups (using one way ANOVA); **p-value‡** associated with dummy variable for group, adjusted for baseline age, sex, blood pressure, cholesterol, glucose, GFR, body mass index, history of myocard infarct, start use RAAS, change on blood pressure, type of statins (for PDD) and PDD (for type of statins) (using multivariate linear regression analysis). **p-value¶** adjusted for all those variables and individual propensity score

DISCUSSION

Our clinical trial data show no effect of a 4-year treatment with pravastatin on UAE nor on GFR. In the observational study a rise in UAE was observed in the subjects that used statins, especially when used continuously, for a longer time and in a higher dose. This rise in UAE was not associated with a statistically significant change in GFR, neither in case of longer duration of use or in case of a higher dose.

How do these data on UAE relate to literature? In both our studies we found no lowering of UAE in subjects using statins, as was suggested from some previous reports [9,10]. Tonolo *et al* [10] reported a 25% reduction of UAE from baseline after simvastatin in 19 normotensive microalbuminuric hypercholesterolemic type 2 diabetic patients. Similar results were observed in the study conducted by Nakamura *et al* [9], in which allocation to cerivastatin was associated with a reduction of UAE in 60 normotensive type 2 diabetics with microalbuminuria and dyslipidemia. Both studies had low sample size and were conducted in hyperlipidemic patients at higher risk for renal impairment. In a recent study in 344 type 2 diabetics, in contrast no effect of either rosuvastatin or atorvastatin on UAE was observed [12]. In our *clinical trial* we found no reduction in UAE, even not when considering that the dose of pravastatin we used was 40 mg, which is relatively high when expressed in DDD: in fact two DDD. Moreover, in our clinical trial the drug was given for a relatively long period of 4 years. In the observational study we even found a rise in UAE among statin users, in particular in association to longer duration of use. These data are in agreement with experimental data that statins may interfere in tubular albumin uptake as a result of the inhibition of HMG-CoA reductase in the proximal tubular cells [6,7]. The discrepancies in both the literature and in our two studies may be explained by either differences in patient characteristics and in the dose and type of statin used. Our clinical trial patients, though older, were in general in better health as expressed by a lower blood pressure, less frequent a previous myocardial infarction, and less frequent use of antihypertensive, lipid- and glucose lowering drugs than in the observational cohort.

How do the data on GFR relate to literature? Our two studies show that statins hardly influence GFR. In the clinical trial no change in GFR was noticed on the statin, whereas in the observational study a modest fall in GFR was observed in the subjects that used statins. This fall in GFR was however not statistically significant after adjustment for differences in baseline characteristics.

These findings contrast to previous suggestions from meta-analyses and post-hoc evaluations. In a meta-analysis of placebo-controlled studies published

before 2001 a beneficial effect of lipid lowering drugs was found on GFR. In this meta-analysis 362 patients with chronic kidney disease were included, divided over 13 studies (of which in 11 studies statins were used). The authors found a lower rate of GFR decline for lipid lowering drugs compared to placebo (difference being 1.9 (0.3 to 3.4) mL / min / year) [18]. In contrast with our patient population, all subjects in this meta-analysis had renal disease, mostly diabetic nephropathy or glomerulonephritis. Athyros et al showed in a subgroup analysis of the GREACE study that treatment with atorvastatin resulted in an increase in GFR, whereas in subjects not using atorvastatin GFR fell. The beneficial effect on GFR was more prominent in the lower two quartiles of baseline GFR and with higher atorvastatin doses [29]. In a subgroup analysis of the CARE study a post hoc analysis similarly found no effect of statins on GFR overall, but in the subjects with the most severe impairment in GFR pravastatin was associated with a less severe fall in GFR during follow up [19]. A subgroup analysis of data from 3 randomized controlled trials in 18.569 subjects with a previous acute coronary syndrome or who were at high cardiovascular risk showed that pravastatin reduced the rate of renal function loss by 8% versus placebo. Again, this effect was greater in subjects with more severe renal impairment [21]. In the URANUS study GFR was not influenced by either rosuvastatin of atorvastatin [12]. Literature so far seems therefore consistent, suggesting that statins may preserve or even improve renal function, especially in subjects with renal disease or more advanced renal function impairment. Since the number of such subjects is low in the PREVEND observational study and the PREVEND-IT randomized controlled intervention study, it might be that consequently in our studies a protective effect of statins on GFR decline could not be shown.

What are the strengths and weaknesses of our data? First, we included data from both a clinical trial and a large observational study. An advantage of using observational drug utilization data is that they reflect routine practice for large and representative populations, in contrast to the much smaller and selected populations in clinical trials [22]. Large observational data allows to extend data in a specific patient categories, that normally are selected for clinical trials. This is true in our clinical trial in which we included subjects with an elevated UAE, with otherwise no indication for statin therapy. This sharply contrast to the general patient population in daily practice that on indication receives statin treatment as in our observational cohort. Indeed, the subjects in the observational cohort study that used statins were more diseased subjects. In our cohort study, the propensity score was used to correct for bias caused by non-randomized assignment between statin users and non-users. Secondly, the observational study allows to study the

impact of duration of use, dose of the drug, and individual drug from the same drug class due to the detailed information regarding drug use during the whole 4 years study period. Third, in both studies we included a sufficient number of statin using subjects to be able to detect a difference in effect of the statin on albumin excretion of less than 1.0 mg/24 hr and on GFR of less than 4.0 ml/min, that is less than 1.0 ml/min/year.

One of the limitations of the study is the fact, that we, at least in the observational study only have data on UAE and GFR 4 years apart. A second limitation is that we are not informed on the actual intake of the drug. In the observational study, our data are based on the delivery of the drug from the pharmacist to the patient. It has however been shown, that such data give reliable information on drug use by the patient [20], especially in case of drugs that have to be used constantly, as is the case for statins. Drugs are delivered for a period of three months, and the patient needs to receive his/her next prescription again after that period. In the clinical trial we checked for compliance every three months, and included in this analysis only data obtained while the patient was still on medication. Third, propensity scores technique can not adjust for residual unmeasured covariates which probably influenced both prescription of statins and clinical outcomes, and thus residual bias is still possible. Finally, our data are limited to subjects with only modest renal damage, that is subjects with an elevated UAE and no more than stage 3 diminished GFR. We feel these data are however of interest for the general nephrologists, as also early renal damage is associated with an impaired renal and vascular prognosis.

What finally, is the clinical consequence of our data? Post marketing surveillance studies frequently bring new effects of a drug under attention, be it positive or negative. In that way we should pay attention to our finding of a rise in UAE in our observational. Though that finding was not confirmed in our randomised controlled clinical trial in fact designed to lower UAE, the data require close attention. This rise in UAE, fortunately was not associated with a fall in GFR.

In conclusion, our data show that in contrast to literature statins do not lower UAE in subjects with only modest renal damage (stage 1-3 CKD), neither in the RCT, nor in the observational cohort study. In the observational cohort study, in contrast, we found a modest rise in UAE related to high daily dose and longer duration of use. Because statins are widely used in the general population our results may be of public health importance and need confirmation in other studies.

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CHAPTER 5

The impact of hormonal contraceptives on blood pressure, urinary albumin excretion and glomerular filtration rate

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ABSTRACT

Introduction

In short-term studies, hormonal contraceptives (HC) suggested to induce a rise in blood pressure (BP) and urinary albumin excretion (UAE), while the effect of HC in renal function (GFR) is still debate. Data on long-term and withdrawal effects of HC-use on these outcomes are however, not available. We therefore studied whether start and cessation of HC induce changes in BP, UAE and GFR.

Methods

We used data from the PREVEND-Study, a prospective cohort of subjects aged 28-75 years. Eligible were women aged ≤ 45 years old with complete clinical and pharmacy data on baseline and follow-up screening (4-yrs later). Multivariate regression analysis was used to estimate the effects of HC on BP, UAE and GFR in those who started (*n*=73), stopped (*n*=117) or continued (*n*=183) with those who never used (*n*=286) as reference group.

Results

BP increased among starters and fell in stoppers. These changes were statistically significant compared to never-users, also after adjustment for relevant variables. UAE increased 14.2% in starters (p=0.074) and fell 10.6% in stoppers (p=0.021), while GFR fell 6.3% in starters (p<0.001) and did not change in stoppers. The effects of stopping HC on UAE and GFR were significantly different compared to changes among never-users, also after adjustment for other variables (p=0.023 and 0.036, resp).

Conclusions

The start of HC is independently associated with worsening of BP, UAE and GFR, while stopping HC-use resulted in an improvement. These data suggest that long-term HC-use (aged 28-45) may be deleterious from cardiovascular and renal point of view, but stopping may result in correction of these effects.

INTRODUCTION

Hormonal contraceptives (HC) have been used for more than three decades. Much attention has been drawn to the thrombo-embolic and cardiovascular adverse events associated with these agents. It is generally acknowledged since 1978 [1] that HC may increase blood pressure. The activation of renin angiotensin system (RAS) which is recently suggested play a role on this mechanism of HC in elevated BP, however, are still in debate [2-5]. Although the association between the use of HC and BP elevation has been repeatedly demonstrated [5-7], few studies showed the beneficial effect on blood pressure after cessation of HC [8-9].

Epidemiological and patophysiological data on HC use and the renal outcome e.g. albuminuria and renal function are limited. Interestingly, some studies have recently described an association between the use of HC and albuminuria [3,5,10]. Higher levels of albuminuria are considered an early marker of vascular endothelial damage [11-12] and are related to an increased risk for progressive renal failure and excess cardiovascular morbidity and mortality [12-17]. The mechanism of HC on UAE is still unknown. Although there are some studies showing that it may be related to a systemic haemodynamic effect, that is a rise in BP [1,9,18] or a specific renal effect [4,19] .

There is currently no evidence suggest that hormonal contraceptives use predispose women to renal disease. However, studies on the association between HC and renal outcome so far have been conducted in a hypertensive [5] or diabetic populations [3]. In the general population data are scarce. Two studies described previously that the use of HC may be associated with an increased risk for microalbuminuria, independent of blood pressure [5,10]. The subjects included in our previous cross sectional study [10] have now been followed for more than 4 years. Participants have been seen for a second screening, and their drug use has been monitored. We now present a prospective, observational study, performed in this cohort of women, investigating whether the long-term use of HC has an effect on BP, albumin loss and glomerular filtration rate.

METHODS

Study design and population

This study is part of the PREVEND (Prevention of REnal and Vascular ENd-stage Disease) study, an ongoing, prospective study which is designed to investigate the impact of urinary albumin excretion on renal and cardiovascular disease progression in the general population. The formation of this cohort study has been previously described in detail elsewhere [10,20]. Briefly, in 1997 a cohort of subjects aged 28-75 years enriched for an elevated urinary albumin excretion was drawn from the population of the city of Groningen. Overall 8592 subjects gave written informed consent and were included in 1997 in the the observational cohort for extensive baseline screening (baseline screening). The 8592 subjects identified of whom 95% caucasians were followed up for cardiovascular and renal morbidity and mortality details since the time of their baseline screening. They were invited for a second screening after a mean follow-up period of 4.2 years (range 2.8-6.1). By then 246 subjects had died, 130 were lost to follow up and 1322 declined participation, leaving 6894 subjects who completed the second screening. Of these 6894 subjects, we only included women in our analysis (*n*=3450). We excluded those subjects who aged >45 years old (*n*=1880) and those for whom no complete information on drug use during follow-up study period (4.2 years) was available (*n*=1129). Thus, 751 subjects are available for further analysis. The shanges in BP, UAE and GFR from baseline compared with the second screening were studied in relation to the use of HC.

Measurement of the study

The methodology used in the PREVEND cohort study has been described previously in elsewhere [10,20]. The screening examinations included two visits to an outpatient clinic, at the first visit an interview is held on demographics, medical history and smoking habits. During a physical examination, weight, height and BP were measured. Body weight was mesured to the nearest 0.5 kg, using a balance scale (seca Vogel & Halke GmbH & C0, Hamburg, Germany) after removal of shoes and heavy clothing. Height was measured to the nearest 0.5 cm using stationer measuring board with right angle. Body mass index (BMI) was calculated as weight in kilogram divided by the square of height in meters. In the supine position, BP in the right arm was measured at 2 visits, every minute for 10 minutes using an automatic blood pressure monitoring device (Dinamap XL Model 9300; Johnson-Johnson Medical Inc, Tampa, Florida). Systolic and diastolic BP was calculated as the mean of the last two measurements at both visits. Fasting blood

samples was drawn for direct measurement of total cholesterol, glucose and serum creatinine. Furthermore urine was also collected during two days for measurement of UAE.

Plasma glucose, serum cholesterol and serum and urinary creatinine were recorded based on findings of an automated dry chemistry analyzer system (Kodak Etachem; Eastmen Kodak, Rochester, NY). Urinary albumin concentration was determined by nephelometry with a threshold of 1.8 to 2.3 mg/l and intra- and interassay coefficients of variation of less than 2.2% and 2.6% respectively (Dade Behring Diagnostic, Marburg, Germany). UAE is given as the mean of the two 24-hour urine excretions. GFR (ml/min/1.73 m2) was estimated using the Modification of Diet in Renal Disease (MDRD) formula: 186 x (serum creatinine) $^{-1.154}$ x (age) $^{-0.203}$ x (0.742 if female) [21].

Information on drug use

Information on drug use was obtained from the InterAction Database (IADB), containing pharmacy-dispensing data from community pharmacies in the city of Groningen. Dutch patients usually register at a single community pharmacy and therefore this pharmacy can provide an almost complete listing of subject's prescribed drugs [22]. Pharmacy data contain, among others, information on the name of the drug dispensed, ATC (Anatomical Therapeutical Chemical) classification, date of prescription and number of days the drug was prescribed and the number of defined daily dose (DDDs) based on definition of WHO [23]. The use of over the counter (OTC) drugs and in-hospital prescriptions are not included. Information on drug use was collected from at least one year prior to the date of the first screening until at least the second screening.

Exposure definitions

Hormonal contraceptives (HC) were defined as preparations containing ethinyl estradiol and/or a progestin, either oral, injection or subcutaneus implant. The Intra Uterine Devices (IUD) and the progestagen-only oral preparations (mini-pill contains low potency progesteron)) are not considered HC in this study.

A subject was defined as using HC at the first screening, if she had used at least one prescription of the drug in the year prior to the first screening. Women who had used HC at the first screening, but stopped its use more than one year before the second screening, were classified as "stopper" (n=117) and those who continued to use it until the second screening (with a mean prescribed daily dose (PDD) during the observation period $\geq$0.75), were defined "continuer" (n=183) (the PDD was calculated from the total amount of DDDs divided by the number of

days exposured). The women who did not use HC at the first screening but started to use it at least a year prior to the second screening, were defined "starter" (*n*=73). Women who had used the hormone for a short period in between the two screenings (intermediate use, *n*=92) were not taken into account in this study. Women who had never used HC in the entire observation period were defined "non users" (*n*=286). We similarly registered the use of antihypertensive medication with a split up in agents interfering in the renin angiotensin system (RAS), such as ACE inhibitors or angiotensin II receptor blockers, and other antihypertensives. Also the use of lipid lowering and glucose-lowering drugs was registered.

Second, we studied subgroups of oral HC users according to their progestin classified as second generation (levonorgestrel, lynestrel, and norethindrone) or third generation (desogestrel, gestodene, and norgestimate) [24]. Subjects who received only one type of HC generation during the study period were included in the subgroup analyses for the type of generation of HC. Subjects who switched from one type HC generation to another were excluded for subgroup analysis for the type of HC generation.

The statistical analysis

Baseline characteristics are reported as mean and standard deviation for continuous variables and as percentage for categorical variables. Because of its skewed distribution, logarithmic transformation of UAE was applied for further analyses and reported values are transformed back to the original scale (geometric means). Differences in population characteristics at baseline between the various groups under investigation were tested for continuous variables by Student's t-test for non-paired data and for categorical variables by a Chi-square test.

We compared the percentage change in BP, UAE and GFR between the first and second screening for each category of HC-user with Student's t-test for paired data. One way ANOVA was applied to test for changes in blood pressure, UAE and GFR between groups with never users as reference. Multivariate linear regression models were built to adjust the baseline parameters that are known to influences changes in BP, UAE and GFR such as age, systolic and diastolic BP, body mass index, cholesterol, glucose, UAE and GFR. Similar analyses were performed to study the association between the various generations of HC and outcome. All calculations were performed with SPSS version 12.0.1 software (SPSS, Chicago, IL, USA). A *p*-value <0.05 was considered statistically significant.

RESULTS

Of the 751 women 342 used HC at the time of the first screening, while 409 women did not. Among the 342 women who used HC at baseline, 117 (34.2%) stopped using the drug before the second screening (*stoppers*), while 183 (53.5%) women were still using it at the time of the second screening (*continuers*) and 42 women used HC less than 0.75 of DDD (*intermediate*). Of the 409 subjects who did not use HC at the baseline examination, 73 (17.8%) started use of HC before the second screening (*starters*), while 286 (69.9%) women never used HC during the entire follow up period (*never users*) and 50 women used HC only for a short period in between the two screenings (*intermediate*). Intermediate users (n=92) were not included for further analysis.

The characteristics of these subjects at baseline according to their HC use at second csreening are presented in Table-1. Women who never used HC were older and had a lower systolic BP and higher GFR compared with those who used or had used HC. Other factors such as diastolic BP, plasma cholesterol, glucose, smoking status, previous myocardial infarction, use of lipid or blood pressure lowering drugs and antidiabetic were not significant different among groups.

The effect of HC on SBP, DBP, UAE and GFR is shown in Table-2. The start of HC was associated with a rise in SBP and DBP, while SBP and DBP fell in *stoppers*. The percentage change in blood pressure among *starters* and *stoppers* was statistically different from the change in the *never users* for both systolic and diastolic BP, also after adjustement for relevant variables.

A similar pattern is also found for UAE. Compared to the first screening, UAE at second screening increased by +14.2% (p=0.074) in *starters* compared to +5.9% (p=0.081) in those who *never used* HC, although the difference between these two groups did not reach statistical significance after adjustment for confounders (p=0.201). In contrast, stopping HC use resulted in a decrease of 10.6% in UAE (p=021). This decrease was significantly different compared to never users, also after adjustment for others variables (p=0.023).

GFR was lower at follow-up visit in *starters* (p<0.001) and *continuers* (p=0.002), but also fell in subjects who never used HC (p<0.001), while GFR in *stoppers* did not change significantly. The fall in GFR was greatest in those who started HC compared to never users and was smallest in those who stopped HC. The percentage reduction in GFR between *stoppers* versus *never users* was significantly different (p=0.036) after adjustment for other variables.

Table-1. Baseline characteristics of the study cohort according to use of hormonal contraceptives (HC)

	Never users n= 286	Starters n= 73	Continuers n= 183	Stoppers n= 117	p-value
Age (years)	39.1 (+/- 4.3)	37.4 (+/- 4.6) *	37.6 (+/- 4.6) *	36.5 (+/- 4.5) *	< 0.001
Body mass index (kg/m^2)	25.0 (+/- 4.4)	24.3 (+/- 3.6)	24.7 (+/- 3.8)	24.2 (+/- 4.3)	0.34
Systolic blood pressure (mmHg)	114.0 (+/- 13.3)	114.8 (+/- 10.5)	117.7 (+/- 13.3) *	114.6 (+/- 12.7)	0.02
Diastolic blood pressure (mmHg)	67.4 (+/- 8.0)	67.8 (+/- 7.5)	69.1 (+/- 7.7)	68.1 (+/- 7.4)	0.17
Glucose (mmol/l)	4.4 (+/- 1.0)	4.4 (+/- 0.6)	4.3 (+/- 0.7)	4.4 (+/- 0.6)	0.71
Cholesterol (mmol/l)	5.1 (+/- 1.3)	5.0 (+/- 1.0)	5.0 (+/- 1.5)	5.0 (+/- 0.9)	0.88
Urinay albumin excretion (mg/24hr)	8.4 (3.9-18.4)	8.3 (4.4-15.4)	9.7 (4.1-23.0)	8.9 (4.5-17.9)	0.23
e-Glomerular filtration rate (ml/min/1.73m^2)	82.1 (+/- 11.9)	81.1 (+/- 13.2)	78.3 (+/- 11.4) *	81.7 (+/- 10.0)	0.01
Smoking (%)	46.8	52.1	52.7	53.8	0.48
History of myocardial infarction (%)	0.7	0.0	0.5	0.0	0.74
Use of lipid lowering drug (%)	0.3	2.7	1.6	1.7	0.29
Use of statins (%)	0.0	2.7	1.6	1.7	0.11
Use of anti-hypertensive (%)	5.9	4.1	5.5	3.4	0.73
Use of renin-angiotensin system inhibitors (%)	1.4	0.0	1.1	1.7	0.74
Use of anti-diabetic (%)	0.3	0.0	0.0	0.0	0.73

*Continuous variables are presented as mean and standard deviation; categorical variables are presented as percentage; urinary albumin excretion is presented as geometric mean and 95%comfidence intervalI; p-value indicates whether mean or prevalence of a certain variable differs between groups (using one way ANOVA for mean and Pearson chi-square for percentage); *p value < 0.05 indicates mean of a certain variable differs between this group compareed with never users using the Tukey test.*

Table-2. Use of hormonal contraceptives in relation to blood pressure urinary albumin excretion and glomerular filtration rate

Type of HC user		1st-screening	2nd-screening	p value*	% change	p-value†
	N	**Systolic Blood Pressure (mmHg)**				
Never users	286	114.0 (± 13.3)	113.9 (± 12.7)	0.838	+ 0.3 (± 8.5)	reference
Starters	73	114.8 (± 10.5)	117.7 (± 12.3)	0.023	+ 2.8 (± 9.1)	0.002
Continuers	183	117.7 (± 13.3)	117.4 (± 14.2)	0.664	- 0.02 (± 8.4)	0.162
Stoppers	117	114.6 (± 12.7)	111.7 (± 12.6)	0.001	- 2.3 (± 7.2)	0.041
	N	**Diastolic Blood Pressure (mmHg)**				
Never users	286	67.4 (± 8.0)	68.1 (± 7.6)	0.035	+ 1.4 (± 8.0)	reference
Starters	73	67.8 (± 7.5)	70.0 (± 7.1)	0.002	+ 3.6 (± 8.5)	0.008
Continuers	183	69.1 (± 7.7)	70.0 (± 8.6)	0.041	+ 1.6 (± 8.6)	0.152
Stoppers	117	68.1 (± 7.4)	67.0 (± 7.5)	0.020	- 1.4 (± 7.5)	0.015
	N	**Urinary Albumin Excretion (mg/ 24hr)**				
Never users	286	8.4 (3.9-18.4)	8.9 (4.0-20.0)	0.081	+ 5.9 (-0.7 / 12.8)	reference
Starters	73	8.3 (4.4-15.4)	9.5 (3.7-23.9)	0.074	+ 14.2 (-1.0 / 31.9)	0.201
Continuers	183	9.7 (4.1-23.0)	9.9 (4.1-24.3)	0.580	+ 2.3(-5.7 / 11.0)	0.809
Stoppers	117	8.9 (4.5-17.9)	8.0 (4.3-14.8)	0.021	- 10.6 (-18.7 / -1.8)	0.023
	N	**e-Glomerular Filtration Rate (ml/min/1.73m2)**				
Never users	286	82.1 (± 11.9)	78.7 (± 13.1)	<0.001	- 4.0 (± 10.7)	reference
Starters	73	80.8 (± 13.2)	75.0 (± 13.2)	<0.001	- 6.3 (± 13.0)	0.074
Continuers	183	78.3 (± 11.4)	76.2 (± 13.2)	0.002	- 2.4 (± 10.9)	0.409
Stoppers	117	81.7 (± 10.0)	80.5 (± 11.0)	0.167	- 1.0 (± 11.3)	0.036

U**rinary **albumin excretion** (UAE) are presented in geometric mean and 95%confidenc einterval; **% change systolic and diastolic blood pressure (SBP and DBP) and estimated glomerular filtration rate (e-GFR)** are presented in mean and standard deviation; **p-value indicates whether UAE, SBP, DBP and e-GFR differs between first and second screening (using paired sample t-test); **p-value†** associated with dummy variable for group, adjusted for baseline age, SBP, DBP, cholesterol, glucose, UAE, and body mass index (using multivariate linear regression analysis); included the use of antihypertensives at baseline in the model did not change the result*

Table-3. Change in blood pressure, urinary albumin excertion and glomerular filtration rate according to different generation of hormonal contraceptives

Type of HC user	2nd-generation of hormone contraceptives			3rd-generation of hormone contraceptives		
	N	**% change SBP**	**p value***	**N**	**% change SBP**	**p-value†**
Never users	286	+ 0.3 (± 8.5)	reference	286	+ 0.3 (± 8.4)	reference
Starters	45	+ 0.4 (± 7.3)	0.379	17	+ 5.3 (± 12.0)	0.004
Continuers	100	- 0.7 (± 7.6)	0.519	30	+ 0.7 (± 7.1)	0.733
Stoppers	67	- 2.5 (± 7.2)	0.045	26	- 0.2 (± 7.9)	0.896
	N	**% change DBP**	**p value***		**% change DBP**	**p-value†**
Never users	286	+ 1.4 (± 8.0)	reference	286	+ 1.4 (± 8.0)	reference
Starters	45	+ 2.1 (± 7.8)	0.282	17	+ 6.1 (± 10.2)	0.010
Continuers	100	+ 1.3 (± 8.6)	0.171	30	+ 0.5 (± 6.6)	0.437
Stoppers	67	- 1.2 (± 7.7)	0.093	26	+ 0.2 (± 7.7)	0.658
	N	**% change UAE**	**p value***		**% change UAE**	**p-value†**
Never users	286	+5.9 (-0.7 / 12.8)	reference	286	+ 5.9 (-0.7 / 12.8)	reference
Starters	45	+14.3 (-7.1 / 40.5)	0.188	17	+19.6 (-6.2 / 52.6)	0.465
Continuers	100	- 5.6 (-15.1 / 4.9)	0.663	30	+ 33.2 (6.4 / 66.6)	0.032
Stoppers	67	- 16.9 (-28.0 / -4.2)	0.011	26	+ 7.5 (-7.0 / 24.3)	0.788
	N	**% change e-GFR**	**p value***		**% change e-GFR**	**p-value†**
Never users	286	- 4.0 (± 10.7)	reference	286	- 4.0 (± 10.7)	reference
Starters	45	- 6.7 (± 13.9)	0.052	17	- 9.2 (± 9.2)	0.058
Continuers	100	- 1.0 (± 11.4)	0.057	30	- 4.8 (± 10.0)	0.422
Stoppers	67	- 1.4 (± 10.0)	0.183	26	- 1.3 (± 14.5)	0.195

HC (hormonal contraceptives); UAE(urinary albumin excretion; mg/24-hr) *are presented in geometric mean and 95% confidence interval;* ***%change SBP and DBP (systolic and diastolic blood pressure; mmHg) and e-GFR (estimated glomerular filtration rate; ml/min/1.73m2)*** *are presented in mean and standard deviation;* ***p-value†*** *associated with dummy variable for group, adjusted for baseline age, SBP, DBP, cholesterol, glucose, UAE, and body mass index (using multivariate linear regression analysis); included the use of antihypertensives at baseline in the model did not change the result.*

When studying the 2nd and 3rd generation contraceptives seperately (Table-3), start of a 3rd-generation HC resulted in an increase in systolic and diastolic BP compared to *never users*. This was not the case among starters of a 2nd-generation HC (*n*=45). On the other hand, subjects who stopped a 2nd-generation HC showed lowering of systolic BP, while stoppers of a 3rd-generation HC had no difference in BP change compared to *never users*. Starting use of either a 2nd- or 3rd-generation HC resulted in an increase in UAE, although these increases were not significant after adjustment compared with *never users*. The rise in UAE was greatest among women who continued the use of 3rd-generation HC (+33.2%) whereas the fall in UAE was most pronounced among subjects who stopped a 2nd-generation HC (-16.9%) and both were significant compared to *never users* after adjusting confounding factors. The changes in GFR among *starters, continuers* or *stoppers* of HC, either a 2nd- or 3rd-generation, were not significant different compared to *never users* (Table-3).

DISCUSSION

We found that the start of HC may induce a rise in SBP and DBP with an albeit insignificant rise in UAE, and fall in GFR. Cessation of the use of HC was associated with a statistically significant fall in SBP, DBP and UAE, and a preservation of kidney function.

This study is the first that evaluates the effect of HC-use on BP and renal outcome in the general population during long-term follow-up and pays attention also to the effect of the withdrawal of HC. Short term studies showed previously that the administration of HC is associated with a rise in BP [5-7]. Ribstein *et al* [5] reported that both in normotensive and hypertensive subjects, HC users had a significantly higher BP compared with non-users. Activation of the renin-angiotensin system (RAS) is considered as an important factor leading to the increase in blood pressure since estradiol administration stimulates the hepatic synthesis of angiotensinogen [2,25]. In another study, Lubianca *et al* [8] reported a significant decrease in SBP and DBP in women who stopped the use of contraceptives compared with those who did not stop. Thus our long-term observational data on blood pressure confirm the findings found in short-term intervention studies.

Regarding the effects of HC on UAE, various short-term studies and cross sectional epidemiological studies have shown an association of HC use and urinary albumin loss [3,5,10]. Our previous study for instance, using data of the first screening of the PREVEND cohort showed that women receiving HC had a 90%

increased risk for microalbuminuria (UAE 30-300 mg/d) compared to non-users [10]. Ribstein *et al* [5] found a significant increase in 24-hour UAE in normotensive as well as hypertensive women using oral contraceptives when compared with non-users. Similar results were observed in a recent study in diabetic population by Ahmed *et al* [3]. These authors reported that in this population 18% of contraceptive users developed macroalbuminuria (UAE > 300 mg/d) compared with 2% in non-users (RR=8.90). Interestingly, in our study a significant reduction in UAE is observed among women that stopped the use of HC, suggesting a reversible effect after discountinuation of HC. This fall in albuminuria was seen in stoppers of 2nd-generation HC but not in women who stopped 3rd - generations HC.

It is of interest that our study is able to give information on age-related changes in renal function over time. It is well known that renal function will decrease with age. We found that, compared to women who never used HC, those who started to use HC tended to have a greater decline in GFR over time, while those who stopped HC had less decline in GFR. At first glimpse this seems in contrast with data from literature that showed that HC users have similar [5] or a higher [3] GFR than non-users. This led to these authors to suggest that HC use may be associated with glomerular hyperfiltration, thus also explaining the risk for microalbuminuria. Our data suggest long term use of HC to induce a fall in GFR. The reassuring finding of our data is however, that these unfavourable effects of HC are reversible after withdrawal, even after many years.

We separetely studied whether these renal effects of HC were seen more in second versus third generation OC. Our data do not permit to draw firm conclusions on this issue, partly because there were only few women on third generation agents. If any conclusion can be drawn, there maybe a tendency that stopping HC use results in an improvement in BP, UAE and GFR in women using second generation HC, while there were no changes observed in stoppers of third generation HC. This may suggest that 3rd-generation HC may be more deleterious than 2nd-generation HC from a renal point of view. This may be in agreement with the data that there is a relationship between HC use and inflammatory markers in particular in women taking 3rd-generation agents. The latter has been argued to contribute to an increased risk for athero-thrombotic [6] and peripheral arterial disease [26]. A recent prospectives cross-over randomized study found no association between second and third generation HC with inflammation marker such as level of serum c-reactive protein [27]. A recent meta analysis conducted by Baillargeon *et al* [28] reported an increased risk of both cardiac and vascular events among 2nd and 3th generation OC users, however, the risk in 3th generation users seems less than in 2nd generation users.

Several potential limitations of the present study have to be considered. Firstly, we could only analyse half of the women who had participated in the previous screening, because approximately 20% of the women withdrew consent and from participating women only 60% had complete information on pharmacy data for the entire study period. However, the baseline characteristics of the women who were lost to follow-up did not differ statistically significant from those who remained in the study, suggesting that loss to follow-up will not be an important source of bias. Second, this study did not include women under 28 years old and a high percentage of our population was current or past smoker at baseline. Third, bias may have been introduced through confounding by indication or contraindication for HC use. This may apply in particular women on 3rd-generation agents, since these preparations were originally introduced to protect against myocardial infarction due to their favourable effect on the lipid profile [29] . The major strength of this study is that we were able to provide the long term prospective follow-up with monitoring of pharmacy records in a large sample of the general population. Furthermore, the design of our study enabled us to compare the effect of HC in women who used HC at first screening but stopped it afterwards, versus subjects who never used these agents, used them continuously, or started the use.

In conclusion, the use of HC on women aged 28 to 45 years old is independently associated with a worsening of BP, UAE and GFR, while stopping HC-use resulted in an improvement. With respect to the generation of HC, our data suggest that third generation agents might be more deleterious than second generation of HC. These data suggest that long-term use of HC may be deleterious from a cardiovascular and renal point of vies, but that stopping may result again in correction of these effects.

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CHAPTER 6

Adherence of pharmacoeconomic studies to national guidelines : an illustration for the Netherlands

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ABSTRACT

Introduction

This study examines the adherence of pharmaco-economic studies for the Netherlands to the Dutch guidelines of conducting a pharmaco-economic evaluation.

Methods

Dutch guidelines for pharmaco-economic research were issued in 1999. All Dutch pharmaco-economic studies that were published in English during 2000-2002 were selected for our review. Two reviewers examined each study for relevance and compared each study with the nine methodological guidelines selected.

Results

We found 29 studies that satisfied inclusion criteria. The societal perspective was assessed in 13 out of the 29 studies (45%), an adequate time period of analysis was chosen in 21 (72%), effectiveness was explicitly differentiated from efficacy in 17 (59%), an incremental analysis was performed in 23 (79%), costs, benefits and health gains were discounted in 24 (83%), effectiveness was expressed in LYGs or QALYs in 16 (55%), reference prices were used in 8 (28%), subgroup analysis was presented in 13 (45%) and sensitivity analysis was included in 26 (90%).

Conclusions

In this review we found the adherence of studies to some of the Dutch guidelines for pharmaco-economic studies is fair. However, major improvements are required with respect to the adoption of the societal perspective, presentation of adequate subgroup analyses and application of reference prices.

INTRODUCTION

Health care expenditures have been rising over the past 10 to 20 years. To lower or sustain the costs for health-care, decision-makers use rational decision-making tools and objective, transparent criteria for reimbursement of new drug therapies. As a result, techniques such as cost-effectiveness or cost-utility analysis are utilised to guide the decision-making process. In a number of countries, in addition to safety, efficacy and quality, a favourable pharmaco-economic profile for new pharmaceuticals is also required to be eligible for reimbursement after market approval [1].

In the Netherlands, the Ministry of Health is intending to use pharmaco-economics as an additional criterium for drug reimbursement commencing 2005. This Dutch policy is in line with other western countries, for instance current reimbursement decisions made in Canada, Australia and the UK, are already partly based on cost-effectiveness.

Careful consideration of pharmaco-economic studies used for the reimbursement of new drugs, require comparable methods to be used. For this purpose, in 1999 guidelines for pharmaco-economic research were developed by the Dutch Health Care Insurance Board [2-5]. According to these guidelines, a pharmaco-economic study must contain a cost-effectiveness analysis and/or a cost-utility analysis next to usual budgetary impact analysis. As of 2005, all new drugs with claimed therapeutic added value must supply a pharmaco-economic evaluation according to the guidelines if applying for reimbursement [1]. In currently, deliverance of a pharmaco-economic file is optional and may be submitted if the manufacturer believes it may help in its strategy reimbursement. These optional studies should adhere to the current pharmaco-economic guidelines.

Our research investigated whether recent pharmaco-economic studies adhered to the pharmaco-economic guidelines in practice or whether deviations exist between practice and theory.

Dutch guidelines for pharmaco-economic research

In this study, we assessed the adherence of pharmaco-economic studies conducted in the Netherlands to the current Dutch guidelines for pharmaco-economic research. By investigating the adherence of studies that were published after the introduction of the guidelines, the relevance of these guidelines for health economists in the Netherlands can be preliminarily assessed. Previously, we investigated whether the guidelines were in line with historical practice; i.e.

whether the guidelines logically came forward from existing studies that have been done prior to the publication of the guidelines in 1999 [1,6-7]. There we noted that for some specific guidelines, Dutch studies were not in line with these specifications (for example, inclusion of indirect cost, discounting of health gains and use of reference prices). Partly these differences between practice and guidelines reflected current controversies among those scientists who conduct such pharmaco-economic studies. For instance, there is still debate on what exact discounting method to choose and how to best assess indirect cost [8-10]. However, despite methodological disputes, a study performed in view of adding valuable information for reimbursement decisions should adhere to the guidelines, be it solely for reasons of comparability. In this study, we will further elicit on the role of pharmaco-economic analysis for policy-making and the role of guidelines in this process.

The Dutch guidelines for pharmaco-economic researches specify recommendations on 19 aspects of which some are of a methodological nature. Others refer to issues concerning the background of the study, affiliation of the study conductors, target audiences and reporting formats.

METHODS

Types of eligible studies and search strategies

A search was conducted of pharmaco-economic studies for the Netherlands that were published in English during 1st January 2000 to 31st December 2002. These studies were published after dissemination of the Dutch guidelines, of course study conduction may have been (partly) before the issued of the guidelines. The elligible criteria for inclusion in this review were (i) pharmaco-economic evaluations (as opposed to evaluations of non-drug related medical interventions); (ii) original research; (iii) full text available investigations, (iv) published in peer review journal. For example, a study on testing for the human papillomavirus was excluded because the subsequent intervention involved (minor) surgery without explicit detail of a pharmaceutical [11]. All cost-effectiveness or cost-utility analyses of pharmaceuticals were included. Most cost-benefit analyses were excluded unless net cost savings were suggested in combination with plausibility of health gains or at least no health losses.

The studies were identified by electronic search. The database used was HIGHWIRE the Library of Science and Medicines (http://highwire.stanford.edu.) The search used the terms “cost (-) effectiveness”, “pharmaco (-) economic(s)” and “(the) Netherlands”.

In this study, we investigated 9 methodological guidelines (out of 19) which reflect the most important criteria for pharmacoeconomic studies and are relatively straightforwardly assessable (Table 1).

Table-1 *The Dutch guidelines for pharmacoeconomic research*

1. Target groups
2. The societal perspective *
3. Timing of the studies
4. Perpetrator of the study
5. Analytical technique
6. Indications (subgroup analysis) *
7. The comparative treatment
8. Incremental and total analysis *
9. Analysis period / time horizon *
10. Efficacy versus effectiveness *
11. Quality of life and utilities
12. Outcomes for cost-utility analysis (LYG or QALY) *
13. Cost identification
14. Cost measurements
15. Cost evaluation using reference prices *
16. Discounting for future outcomes and costs *
17. Reliability and validity (sensitivity amalysis) *
18. Reporting the studies
19. Modelling of the results

* selected for this review

Our guideline states that analyses should be conducted primarily from a societal perspective, including both direct medical costs / benefits, direct non-medical costs / benefits (for example travel costs), and indirect costs [3]. The Dutch guidelines explicitly state that the most important feature of the societal perspective is the inclusion of the indirect costs from production losses. In contrary to pharmaco-economic guidelines in other countries, production losses should be valued using friction costs methodology instead of the human capital approach [12].

Obviously, an adequate time horizon should be deployed to capture all relevant aspects of cost, benefits and health effects. If modelling of future developments is required, structure and motivation of the model should be

explicitly provided. In this respect, we note that the full impact of pharmacotherapeutic interventions in infectious diseases, where cure of individual patients may lead to a reduced spread of the infection. Hence, to further reduce the prevalence of the infection as an indirect effect, can only be realised with longer term study (for example, detection and treatment *Chlamydia trachomatis*) [13].

In addition, the guideline states that explicit distinction should be made between efficacy (as often-measured in clinical trials) and effectiveness (in real word circumstances). Effectiveness involves performance of the drug in actual clinical use, whereas efficacy may involve highly selected populations included in the clinical trial. If efficacy is used as an estimate for effectiveness, plausibility of this assumption should be explicitly motivated. If efficacy and effectiveness are suspected to significantly deviate and no data on effectiveness are available, modelling should be used to extrapolate efficacy data to effectiveness.

Incremental cost-effectiveness ratios should be reported, comparing the relevant alternatives. In principle, comparison of the investigated drug should be with the standard (evidence-based) treatment. Standard treatment is often interpreted as the guideline treatment that is recommended by clinical practitioner's [14].

Costs, benefits, and health effects distributed over time should be discounted at an annual rate of 4%, prior to aggregation. Discounting of the future costs and benefits is a standard feature of economic evaluations and no debate on that exists. Discounting of health effects is still heavily debated [8-10].

Health effects should ideally be expressed as life-years gained (LYGs) or quality-adjusted life years (QALYs). The rationale behind the preference for these outcome measures is that health outcomes are made comparable. This is not the case for other outcomes - such as infections averted, complications averted and cases cured - as these other outcomes are often dependent on the specific disease with respect to severity.

Reference prices should be used as listed in the Dutch manual on costing in economic evaluation [15]. These reference prices are estimated cost prices as far as possible. For example, such national average cost price estimates exist for inpatient days, hospital outpatient contacts and GP visits. For branded and generic drugs market prices should be used including the pharmacist's fee. In case of absence of approriate cost price estimates, tariffs may be used.

Table-2. Pharmaco-economic studies for the Dutch situation found eligible for analysis of adherence to the Dutch guidelines for pharmaco-economic research.

Authors	Ref	Disease area	Drug(s)
Van Os N, et al [2000]	18	Diabetes nephropathy	ACE Inhibitors
Welte R, et al [2000]	13	Chlamydia trachomatis	Azithromycin
Stolk EA, et al [2000]	19	Erectile dysfunction	Sildenafil versus papaverine
Joosen EAM, et al [2000]	20	Helicobacter pylori	Ranitidine
Postma MJ, et al [2001]	21	Pneumococcal infection	Polysacharide vaccine
Van Hout BA, et al [2001]	16	Hyperlipidemia	Statins
Pinto CG, et al [2001]	22	Allergic conjunctivitis	Emedastine vs.levocabastine
Bos JM, et al [2001]	23	HIV and STD	Highly Active Anti Retroviral
Bos JM, et al [2001]	24	Meningococcal infection	Meningococcal vaccine
Nuijten MJ, et al [2001]	25	Parkinson's disease	Entacapone
Jansen R, et al [2001]	26	Toenail onychomycosis	Itraconazole vs terbinafine
Doyle JJ, et al [2001]	27	Acute major depression	Venlafaxine, SSRI's and TCAs
Muller E, et al [2001]	28	Pressure sores	Collagenase ointment
Van Valkengoed IGM [2001]	29	Chlamydia trachomatis	Azithromycin
Krijnen P, et al [2001]	30	Arthritis	Antibiotics
Van den Boom G, et al [2001]	31	Obstructive airway	Fluticasone
Nuijten MJ, et al [2001]	32	Major depression	TCAs versus SSRIs
Postma MJ, et al [2001]	33	Chlamydia trachomatis	Azithromycin
De Bock GH, et al [2001]	34	Acute sinusitis	Antibiotics
Nuijten MJ, et al [2001]	35	Rheumatoid arthritis	Etanercept versus infliximab
Li N, et al [2001]	36	Breast cancer	Chemotherapy
Oostenbrink JB, et al [2001]	37	Infranguinal bypass	Aspirin
Lindgren P, et al [2002]	38	Breast cancer	Exemestine vs. megestrol
Hartman M, et al [2002]	39	Psoriasis	Dithranol
Postma MJ, et al [2002]	40	Neural tube defects	Folic acid
Ten Berg JM, et al [2002]	41	Coronary angioplasty	Coumarins
Caro JJ, et al [2002]	42	Alzheimer's disease	Galantamine
Schermer TR, et al [2002]	43	Asthma	Budesonide
Van Agthoven, et al [2002]	44	Chronic rhinosinusitis	Filgastrim

Subgroup analysis should be presented additionally in case of potentially important differences in clinical effectiveness or costs among groups. For example, the cost-effectiveness analysis of statins in patients renal insufficient should ideally encompass estimates of relevant clinical subgroups such as type 1 and type 2 diabetes patients and non-diabetic renal disease [16]. Furthermore, specific age groups should often be considered separately, beacuse complications may considerably differ between younger and older patients. For example, evaluation of influenza vaccine is more cost-effective in elderly [17].

As conditions and assumptions are often uncertain, a sensitivity analysis must be undertaken,. This should encompass at least a univariate sensitivity analysis; multivariate analysis is optional in the guidelines. If the reporting format doesn't allow extensive sensitivity analysis to be shown, at least a summary should be presented with the full analysis being available in background files (available on request).

Two reviewers examined each study for inclusion. The same two reviewers independently evaluated each study with regard to adherence of the nine methodological guidelines selected and resolved any disagreement by discussion.

RESULTS

Using the term words, 132 studies were found to be potentially relevant. Applying the inclusion criteria to those studies, twenty-nine were included in our review (Table-2). Most of the excluded studies were either cost analyses only or referred to non-drug related medical interventons. The adherence to the guidelines from the indentified study is shown in figure-1.

High adherence to the guidelines were found for incremental analysis, discounting and sensitivity analysis. An incremental analysis was performed in 23 studies (79%). Twenty-four studies (83%) performed 4% discounting for costs, benefits and health gains. Other studies applied a discount rate that is not recommended by the Dutch guideline or choose not to discount health gains. Sensitivity analysis was adequately reported in 26 studies (90%).

An adequate time period of analysis was chosen in 21 studies (72%). Effectiveness was explicitly differentiated from efficacy in 17 studies (59%) and effectiveness was expressed in LYGs or QALYs in 16 studies (55%).

The societal perspective was included in 13 studies (45%). Most of the studies were conducted from third-party payer, provider, health-care or hospital perspective. Subgroup analysis was mostly not taken into account. The Dutch

manual on costing in economic evaluations was used as a source for reference price in only 8 studies (28%).

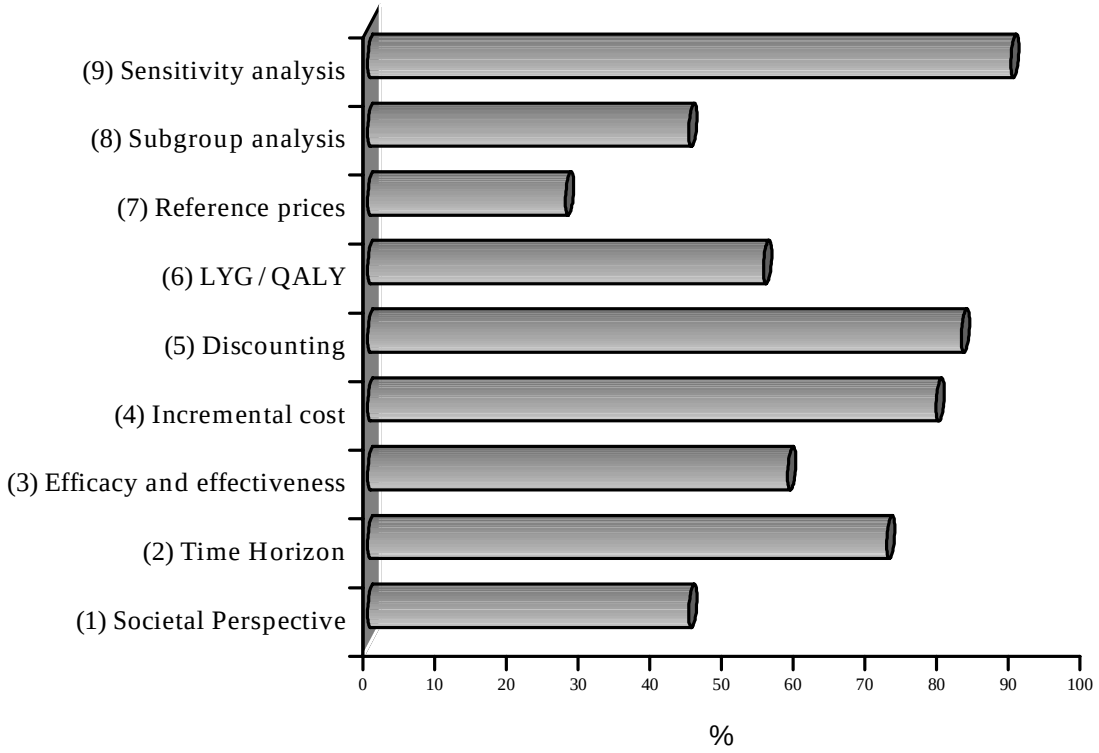

Figure-1. Adherence (in percentage) of included studies to nine selected guidelines for pharmaco-economic research

No studies adhered to all nine criterias, and the median number of criterias to which studies adhered was six. There were two studies adhering to the eight of the 9 selected methodological guidelines. Finally, we found that if excluding the six studies that were published by our research group, there was no sugnificant different in the results.

DISCUSSION

This review compares published pharmaco-economic studies for the Dutch situation with selected Dutch guidelines for pharmaco-economic research. Fair to good adherence (50% or more) was found in most of the methodological guidelines: these are (i) time horizon, (ii) efficacy versus effectiveness, (iii) incremental analysis, (iv) discounting, (v) LYG or QALY as outcome, and (vi) sensitivity analysis. Our analysis also showed that for some methodological aspect compliance with the

existing guidelines remains poor: (i) perspective, (ii) reference price and (iii) subgroup analysis.

Most studies have an adequate time horizon. The appropriate time horizon is related to (i) the duration of the clinical condition and (ii) the duration of (the effects of) the intervention. In some cases, acute disease, the clinical duration will be a matter of days or weeks, in others, such as chronic disease, the duration may be lifetime [45]. Furthermore, it is important that the all-relevant downstream consequences of particular medical intervention are accounted for in the analysis. This is for example the case for infant vaccination against measles, where the continous intervention influences the spread and prevalence of the infection and cost-effectiveness over time [46].

Studies that had a time horizon exceeding 1 year mostly used 4% discount rate for monetary amounts. In five studies health gains were not discounted or other rates were used. Often in sensitivity analysis other discount rates were investigated, such as 3% (USA-standard) and 5% (often applied in “older” studies).

Several studies in this review applied an adequate incremental analytic framework and explicitly distinguished efficacy and effectiveness. Most of the studies discussed multiple and this frequently included LYGs and QALYs. In 13 studies neither LYGs nor QALYs were used. For example, for interventions in *Chlamydia trachomatis* "major outcomes averted" were used to express effectiveness [33]. These included infertilities and ectopic pregnancies, however no attempt to transform these into QALYs was undertaken.

The most notable divergence from the guidelines were on the issues of perspective and references prices. While the Dutch guidelines recommend a societal perspective, most studies used a narrower, provider's or health-care perspective; i.e, a third-party payer perspective. There are numbers of reasons for this, the most important being that many studies were commissioned to help in formulary reimbursement decisions. Also, the sponsor (for example, pharmaceutical industry) may have influenced the choice of the perspective [47]. Therefore, relevance to adhere to an individual guideline also depends on the specific purpose of the study (sponsored research for reimbursement, investigation to support hospital budgeting or assessments for the Ministry of Health).

Although many guidelines agree on how costs should be reported, there is substantial variation in which costs should be included. The Dutch guideline states that societal perspective, direct and indirect cost such as production loss should be included. Production losses should be valued by the friction cost approach.

Table-3 Comparing the Dutch, Canadian and Australian guidelines for the selected methodological issues.

Selected guidelines	Dutch guidelines	Canadian guidelines	Australian guidelines
Perspective	Societal prospective	Perspective of decision makers and / or societal perspective	Perspective of society
Time horizon	The time horizon of the study must be enables valid and reliable to capture all relevant aspects of costs and effects.	based on currently empirical data and long enough to structure all relevant outcomes and costs	Related to the treatment pattern and natural history of the disease
Efficacy and effectivenss	Effectiveness rather than efficacy	Effectiveness rather than efficacy	Effectiveness in natural units
Incremental analysis	Cost and effect must be reported in the form of incremental values	Incremental cost, clinical outcomes, cost utility and cost-effectiveness	Incremental cost, incremental outcomes and incremental cost-effectiveness
Discounting	Future outcomes and costs should be discounted at equal rates. Current discount rate in Netherlands is 4%. Also use 0%, 3% or 5% in sensitivity analysis.	Discount rate at present is 5%	Cost or benefit are discounted at an annual rate of 5%
Outcome	QALY or LYG	QALY or Willingness To Pay (WTP).	LYG, or QALY gained
Reference prices	Manual for cost research. Methods and recommended prices for economic evaluations in health care. Edited by the Council for Health Insurance, Amstelveen.	Unit prices for resources need to be estimated in Canada, but may allow for the use of quantities of individual services to be estimated from non-Canadian studies.	Manual of resource items and their associated costs.

Continued tabel-3

Selected guidelines	Dutch guidelines	Canadian guidelines	Australian guidelines
Subgroup analysis	The subgroup analyses for patient groups, disease subtypes, degree of seriousness, presence or absence of comorbidity, etc., must all be stated.	Generalizability to various subgroups	Not applicable
Sensitivity analysis	When conditions and assumptions are uncertain, at least univariate sensitivity analysis using different discounting rates	Sensitivity analyses are used to assess the robustness of the qualitative conclusions and identify areas where further research is needed to more precisely.	One way and two way sensitivity analysis, using different discounting rates or substituting the upper and lower 95% confidence limits of the difference in outcomes achieved.

As for indirect cost, the Australian guideline discourages their inclusion, whereas the Canadian guidelines recommend measuring the human capital approach to production losses [2]. Furthermore, a comparison of the Dutch, Australian and Canadian guidelines show that they were in aggreement for most of the 9 selected methodological aspect [3,48-49] (Table-3).

With respect to references price, the guideline recommends the use of a list of standard costings, however most of the studies used a variety of sources that were often established specifically for the study. Sometimes, the estimated cost prices were based on one (several) local hospital(s) instead of one national average as is specified in the manual on costing.

The increasing trend in the number pharmaco-economic studies performed raises concerns on many issues surrounding the quality of research, such as misuse of terminology, lack of standardization and inability to generalize results. These issues cause potential bias in results and inadequate reporting formats [48]. Guidelines for pharmaco-economic research help to assess quality of economic studies, to address methodological problems and support on ethical and

reimbursement issues. Guidelines benefit (i) researchers in performing high quality and scientifically valid studies, (ii) users to properly assess and interpret evaluation studies, (iii) companies in making submissions to the government for drug reimbursement decisions, and (iv) individuals interested in assessing and applying research results [50-51]. If guidelines are followed, the capacity of decision makers is enhanced to appreciate the underlying methods used, the validity of inferences, judgements about the cost and outcomes as reported in the economic evaluation of health care technologies [50]. However, internationally, the use of pharmaco-economic guidelines is not uniformly accepted or considered feasible in several countries [47, 50-52]. Remaining inconsistencies hamper interpretation with respect to the actual perspective chosen, cause difficulties to implement economic results or extrapolate them to other regions/institutions, enhance variability in resource management and practice patterns, and outcome variables may not be correctly measured or important variables ignored [47, 50-52].

We note that on the one hand guidelines enhance standardisation and comparability, whereas on the other hand they may lead to restrictions on the individual researcher's freedom in choosing the preferred design. However, in Canada, two years experience with the guidelines demonstrated that except for the perspective of the analysis, guidelines were adhered to and did not restrict investigators to specific methodologies or techniques [47].

CONCLUSION

The adherence to National guideline from recent published Dutch pharmaco-economic study is fair. This finding is in line with investigations on guideline adherence in other countries (e.q. Canada). However, major improvements are required with respect to the adoption of the societal perspective, presentation of adequate subgroup analyses and application of reference prices.

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CHAPTER 7

Cost-effectiveness of screening for albuminuria with subsequent fosinopril treatment to prevent cardiovascular events: a pharmacoeconomic analysis linked to the PREVEND and PREVEND-IT study

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ABSTRACT

Introduction

This study estimated the cost-effectiveness, from the Dutch health care perspective, of screening for albuminuria in the general Dutch population to prevent cardiovascular events (CVEs) with subsequent angiotensin-converting enzyme inhibitor treatment, using data from the Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND-IT).

Methods

PREVEND-IT was a single-center, double-blind, randomized, placebo-controlled trial with a 2 × 2 factorial design within the larger observational Prevention of REnal and Vascular ENdstage Disease (PREVEND) study. The PREVEND-IT study was conducted to assess the effects of fosinopril 20 mg and pravastatin 40 mg on CVEs in subjects with inclution criteria: urinary albumin excretion (UAE) rate in the range from 15 to 300 mg/d, blood pressure <160/100 mm Hg, and plasma cholesterol level <8.0 mmol/L. Cost-effectiveness estimates for the Dutch population were expressed in euros (2002; 1€ = 1.01 US$) as net costs per life-year gained (LYG) in the baseline and sensitivity (stochastic) analyses.

Results

Data were assessed for 864 subjects, with a mean (SD) follow-up of 46 (±7) months. CVEs occurred in 45 (5.2%) subjects. Subjects who received fosinopril had a 40% lower incidence of CVEs than subjects in the placebo group (3.9% *vs* 6.5%, respectively; *p*=ns). The cost-effectiveness of screening for albuminuria was determined to be €16,700/LYG for the study population. Stochastic analysis indicated that the probability of the cost-effectiveness being below the suggested Dutch threshold of €20,000/LYG was 59% in the baseline analysis. The probability of cost-effectiveness would increase to 91% if subjects with UAE >50 mg/d were treated with fosinopril. Limiting the screening to subjects aged >50 years and >60 years also improved cost-effectiveness.

Conclusions

The results of our study suggest that screening the general Dutch population for albuminuria and subsequently treating those found positive with fosinopril may be cost-effective compared with placebo from the Dutch health care perspective. Confirmation from larger multicenter trials is needed.

INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of death in many countries [1,2]. In the Netherlands, CVD accounts for ~11% of all health care costs [3]. Microalbuminuria, defined as a slightly elevated albumin level (urinary albumin excretion (UAE) >30 and <300 mg/d), is a marker associated with an increased risk for cardiovascular (CV) morbidity and mortality in subjects with diabetes [4,5] or hypertension [6], and in the general population [7–9]. Screening for microalbuminuria, either alone or in combination with screening for hypertension and hypercholesterolemia, may be a useful tool to identify subjects at risk for CVD and/or progressive renal failure [10]. Use of antihypertensive agents has been shown to be effective in reducing the incidence of cardiovascular events (CVEs) [11]. Antihypertensive interventions, particularly with angiotensin-converting enzyme (ACE) inhibitors, have been reported to lower UAE in subjects with or without diabetes, and in those with essential hypertension [11,12]. However, it is not known whether an intervention focusing specifically on the reduction of UAE will result in a decrease in CVEs. Therefore, the Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND-IT) [13] was designed to assess the effects of an ACE inhibitor on the incidence of CVEs in subjects with elevated UAE.

Various trials have reported the benefits of CVD prevention. In studies reporting the cost-effectiveness of secondary prevention [14–18], most have found favorable cost-effectiveness for the use of ACE inhibitors in preventing CVEs in high-risk subjects. However, there have been few investigations of their cost-effectiveness in primary prevention, particularly with respect to nephrology markers [19,20]. Prevention based on albuminuria measurement in the general community may be an option for primary prevention. Golan *et al* [21] reported that treatment with ACE inhibitors in subjects with macroalbuminuria (UAE >300 mg/d) and diabetic nephropathy was cost-effective in preventing end-stage renal disease. Palmer *et al* [22] found that the use of angiotensin-receptor antagonists in subjects with diabetes was more cost-effective compared to other antihypertensive to improve life expectancy if treatment was started during the early microalbuminuria stage (i.e. UAE >30 mg/d). However, Boulware *et al* [23] found that screening the general population for albuminuria was not cost-effective when considering renal outcomes (end stage renal desease). As of the time of writing, no cost-effectiveness study has been directed at the prevention of CVE (PubMed; up to 2005; key words: cost-effectiveness, albuminuria, cardiovascular disease. Therefore, the present study aimed to investigate the cost-effectiveness of

screening for albuminuria to prevent CVE with ACE-inhibitor treatment using data from PREVEND-IT [8,13,24–25].

PREVEND-IT compared the effect of the ACE-inhibitor fosinopril and the 3-hydroxy-3-methylglutaryl coenzyme A–reductase inhibitor pravastatin on the incidence of CVEs in subjects with albuminuria (>15 mg/d) and normal blood pressure and serum cholesterol levels [13]. During a 4-year treatment period, fosinopril was associated with a significant reduction in albuminuria compared with placebo (20.9% decrease *vs* 4.7% increase, respectively; $p<0.001$) and numerically fewer CVEs (p=ns). The fosinopril group had a 40% lower incidence of CVEs compared with the placebo group (number needed to treat [NNT], 38). Subjects with microalbuminuria (>50 mg/d) had a 60% lower incidence of CVEs than those in the placebo group (NNT, 13). Pravastatin treatment was not associated with a significant reduction in albuminuria or a significant change in the incidence of CVEs (4.8% in pravastatin *vs.* 5.6% in placebo; Hazard ratio 0.87 [0.49-1.57]). Because the present analysis was based on the nonsignificant trend toward fewer CVEs with fosinopril in PREVEND-IT, it should be interpreted as a hypothesis-generating study whose findings need confirmation in larger multicenter trials.

PATIENTS AND METHODS

PREVEND and PREVEND-IT

The design and principal results of PREVEND-IT [23] and the Prevention of REnal and Vascular ENdstage Disease [25] (PREVEND) study have been reported in detail elsewhere. PREVEND-IT is part of the ongoing PREVEND study [8,24], and subjects for PREVEND-IT were recruited from the PREVEND study. The PREVEND trial was designed to study the impact of albuminuria levels on CV and renal morbidity and mortality in the general Dutch population. In 1997–1998, the prescreening phase began when all inhabitants of the city of Groningen aged 28 to 75 years (n = 85,421) were invited to send in a morning urine sample for measurement of the urinary albumin concentration (UAC) and to complete a questionnaire on demographic characteristics and CV history (Figure-1). Responses were received from 40,856 persons. Based on their UAC, subjects were invited for further study. Of the 40,856 responders, 9966 had a UAC ≥10 mg/L. Excluded from further study were diabetic subjects (n = 167), pregnant women (n = 60), and those who declined to participate (n = 3739). Two urine samples were collected in a 24-hour period from each of the remaining 6000 subjects. Of the final group of subjects, 3964 had normal UAE (<15 mg/d), 1105 had high-normal UAE (15–30 mg/d); 931 had

microalbuminuria (UAE 30–300 mg/d), including 498 with high microalbuminuria (UAE 50–300 mg/d); and 82 had macroalbuminuria (UAE >300 mg/d) [26]. These subjects were invited to the outpatient clinic for testing and further assessment of CV risk factors and CV and renal morbidity.

Formal inclusion criteria for the PREVEND-IT study were persistent albuminuria (1 UAC measurement >10 mg/L and ≥1 UAE measurement of 15–300 mg/d), blood pressure <160/100 mm Hg (threshold for normal blood pressure according to Dutch guidelines at the time of the design of the study) [27], no use of antihypertensive or lipid-lowering drugs, and total cholesterol <8.0 mmol/L (<5.0 mmol/L in the case of previous myocardial infarction).

Eight hundred sixty-four subjects who fulfilled the inclusion criteria were willing to participate in the study. These subjects were randomized to receive fosinopril 20 mg, fosinopril placebo, pravastatin 40 mg, or pravastatin placebo in a 2×2 factorial design.[13] The primary end point of PREVEND-IT was the incidence of CVE, defined as CV mortality, nonfatal myocardial infarction or myocardial ischemia, heart failure, peripheral vascular disease, or cerebrovascular attack.

The CVE rate in the PREVEND-IT population was estimated at ~15%. The planned sample size of 450 subjects in each arm (450 fosinopril *vs* 450 placebo or 450 pravastatin vs 450 placebo, based on the 2×2 factorial design) provided a power of ~80% to detect a significant difference in the incidence of CVEs between the active-treatment and placebo arms [13].

Subjects included in PREVEND-IT had a mean (SD) age of 51 (±2) years, and 65% were male. They had relatively normal systolic and diastolic blood pressure (130 [±18]/76 [±10] mmHg) and cholesterol levels (5.8 [±1.0] mmol/L). Median UAE was 22.8 (15.8–41.3) mg/d. During follow-up (46 [±7] months), the primary end point occurred in 45 (5.2%) subjects, 17 (3.9%) in the fosinopril group (n = 431) and 28 (6.5%) in the placebo group (n = 433) (hazard ratio, 0.60; 95% CI, 0.33–1.10; p = 0.098, log-rank test). Because of the 2×2 factorial design, patients in both the fosinopril and placebo groups also may have received pravastatin (Figure-1, Table-1). In post hoc analysis, this effect differed in subjects with a UAE >50 mg/d who received fosinopril, whereby a relative risk reduction in CVEs of up to 60% was observed (5.2% *vs* 13.0%; p=ns). Also, a significantly worse prognosis for event-free survival was associated with a UAE >50 mg/d in subjects receiving placebo (p = 0.008). The primary end point occurred in 21 (4.8%) subjects in the pravastatin group (n = 433) and 24 (5.6%) subjects in the placebo group (n = 431) (hazard ratio, 0.87; 95% CI, 0.49–1.57; p=ns).[13]

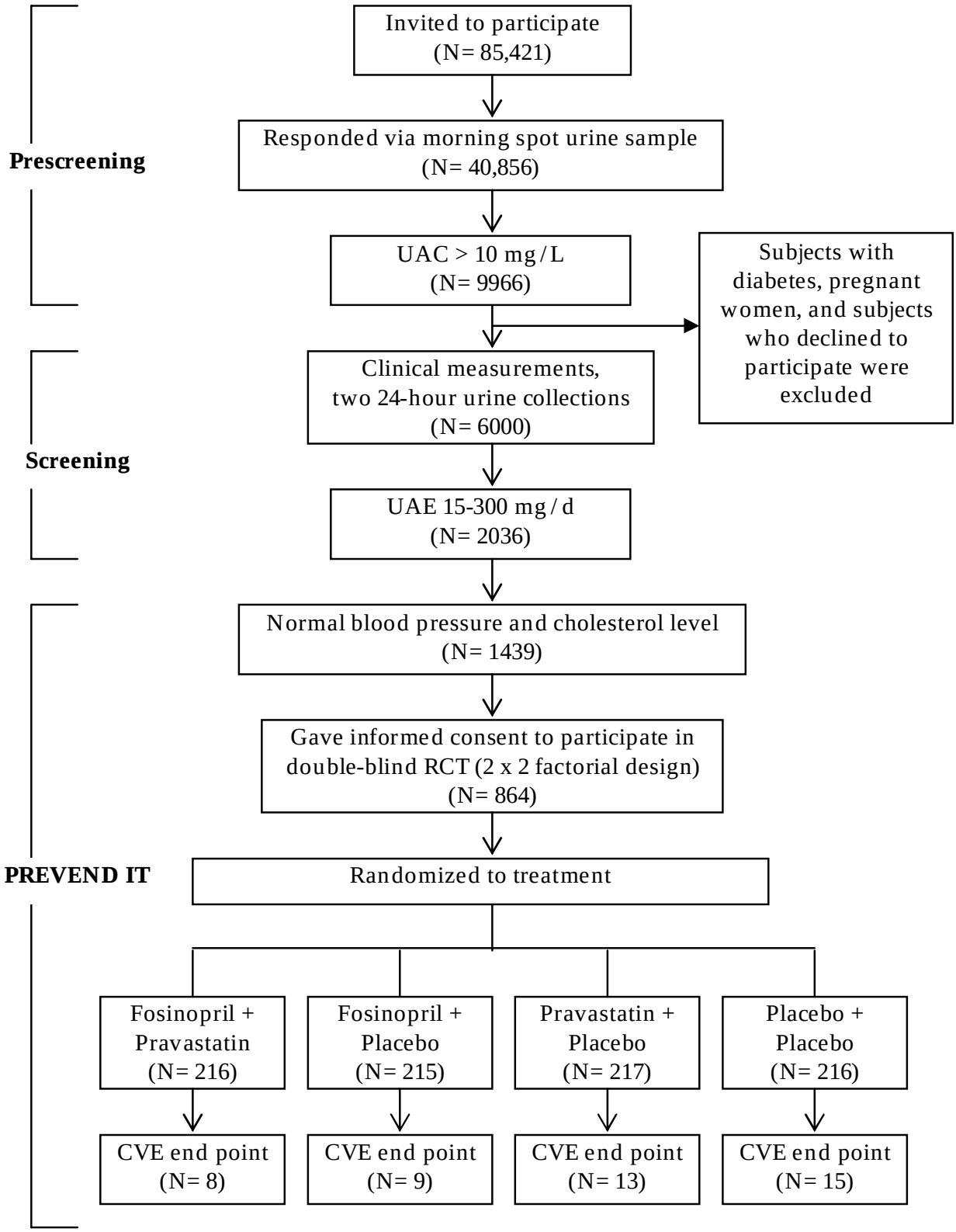


***Figure-1**. Flow chart of the design and subjects experiencing the primary end point (a cardiovascular event [CVE]) of PREVEND IT (Prevention of REnal and Vascular ENdstage Disease Intervention Trial); UAC = urinary albumin concentration; UAE = urinary albumin excretion; RCT = randomized clinical trial.*

Table-1. Primary end points of the Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND-IT)

Primary End Point	**Fosinopril (n = 431)**	**Placebo (n = 433)**
Cardiovascular death	3	3
Nonfatal myocardial infarction	12	11
- percutaneus transluminal coronary angioplasty (PTCA)	5	4
- coronary arterial bypass grafting (CABG)	4	2
Heart failure	0	2
Peripheral artery disease	1	2
Cerebrovascular disease (stroke)	1	10
Total cardiovascular events	**17**	**28**

Study Design

The present study was a cost-effectiveness analysis with a focus on net costs per life-year gained (LYG) [28,29]. In all calculations, fosinopril treatment was assumed after detection of a UAE above the defined threshold. In the baseline analysis, this threshold was set at 15 mg/d. For efficacy, subjects receiving fosinopril (*n*=431) were compared with subjects receiving placebo (*n*=433), regardless of the receipt of pravastatin treatment in the 2×2 factorial design. This approach optimized the number of subjects included in the economic analysis. In the sensitivity analysis, cost-effectiveness was analyzed based on age (>50 years and >60 years [13]), and the cutoff for albuminuria was varied (>30 and >50 mg/d).

The study adopted the Dutch health-care perspective and focused on the costs of hospital resource use for CVEs: hospitalizations, diagnostic tests, and therapeutic procedures. Additionally, the estimated costs of screening and fosinopril treatment were included. Patient-level data on resource use were collected over the full period of study follow-up. All costs were expressed in 2002 euros.

Costs

Screening costs were estimated based on data from the PREVEND study (Table-2). The costs of inviting 85,421 persons to take part in the prescreening program and of prescreening 40,856 persons were €62,700 for apparatus, €76,800 for administration, €61,800 for laboratory materials, and €81,400 for personnel. The costs of the subsequent screening program were €73,600 for apparatus, €9100 for administration, €90,000 for laboratory materials, and €328,200 for personnel. Personnel costs related to research (epidemiologists and statisticians) were excluded, as these would not be part of the routine screening program for which cost-effectiveness was estimated. The total costs of the prescreening and subsequent screening programs were €783,600. The costs of identifying 1 person with a UAE between 15 and 300 mg/d were estimated at €385. Limitation of treatment to those with a UAE of >30 mg/d and >50 mg/d was associated with a higher cost of identifying 1 such person (€842 and €1574, respectively).

The costs of fosinopril were based on actual consumption during the study follow-up period. The costs of general practitioner (GP) visits (€18/visit) and pharmacist's fees (pharmacy charges associated with dispensing the prescription; €6/prescription per 3 months) were also taken into account. No visits to the GP were assumed for adverse effects of fosinopril. The costs of medication were obtained from the 2002 Dutch Pharmacotherapeutic Guidelines [30].

Table-2. Costs of screening for albuminuria in the general Dutch population, based on the Prevention of REnal and Vascular ENdstage Disease study

Screening Stage	**Costs Year-2002 €**
Prescreening (*n* = 85,421 subjects)	282,727
Screening (*n* = 6000 subjects)	500,909
Identification of 1 person with a urinary albumin excretion above the specified threshold	
>50 to <300 mg/d (n = 498 subjects)	1574
>30 to <300 mg/d (n = 931 subjects)	842
>15 to <300 mg/d (n = 2036 subjects)	385

Hospital costs associated with diagnostic and therapeutic procedures for CVEs corresponding to the primary end points were derived by multiplying resource use by unit costs taken from Dutch tariffs [31]. Daily inpatient costs on a regular ward were €199 in a general hospital, €279 in an academic hospital, and €889 for an intensive care unit, based on Dutch reference prices for pharmacoeconomic evaluations [32,33]. These costs included specialist, resident physician, and nursing fees; laundry; nutrition; accommodation and cleaning; overhead; and equipment [32]. Costs for outpatient visits were €40 in a general hospital and €70 in an academic hospital [33]. Patient-specific costs for medications other than the study drugs received during hospitalization were not explicitly included (mean costs for nonspecific patient medications are incorporated into the cost of the inpatient hospital day). Every subject with a reported CVE had different total hospital costs, depending on individual diagnostic and therapeutic procedures, length of hospital stay, and number of visits to the outpatient clinic.

Table-3. Remaining life expectancy at various ages in the general population* and in subjects who have had a cardiovascular event (CVE).†

Age	General Population, years	After a CVE, years
Men		
50 years	27.8	15.9
60 years	19.3	12.3
70 years	12.1	8.8
80 years	6.8	5.3
Women		
50 years	32.4	20.3
60 years	23.5	16.1
70 years	15.4	11.0
80 years	8.7	7.0

**Dutch life tables.[33]*
†Framingham life tables adapted to the Dutch population.[2]

Cost-Effectiveness Analysis

The cost-effectiveness ratio (CER) was expressed in net costs per LYG. Net costs resulted from the costs of screening and fosinopril treatment minus the benefits of averted costs related to averted events (ie, screening/treating vs no screening/"doing nothing"). Calculation of LYG was based on losses in the remaining life expectancy of subjects with CVEs in both groups (fosinopril and placebo). Loss in remaining life expectancy after a CVE was estimated using a Dutch adaptation of data from the Framingham Study [2] and standard Dutch life tables (data for 1998–2002, Central Bureau of Statistics) [34]. Table-3 lists these assumptions (interpolations were used for ages between those presented). Monetary amounts and LYG were discounted at 4%, according to Dutch guidelines for pharmacoeconomic research [35].

Statistical Analysis

Bootstrapping of PREVEND-IT data (10,000 replications) was used to derive 95% CIs for the CER and threshold probabilities [36–38]. The bootstrap calculation was perforemd with S-Plus version 7.0 software (Insightful corporation, Seattle, WA) Parametric bootstrapping was used, assuming a bivariate normal distribution for mean net costs and mean effect (life-years) [28,39] . To describe the uncertainty in estimates of the CER, we constructed acceptability curves [40]. These curves show probabilities that the screen-and-treat intervention is acceptable given a specific threshold, above which the CER is considered unfavorable and below which it is considered favorable. In cost-effectiveness acceptability analyses, we report the median CER and the percentage corresponding to €20,000/LYG, as this figure is the only published threshold for the Netherlands (no formal threshold exists in the Netherlands for cost per quality-adjusted life year (QALY) [41]. However, this threshold is subject to controversy and its use should be interpreted with caution [42,43].

Sensitivity Analysis

Sensitivity analysis was directed at the performance of the intervention in various subgroups and the potential for targeted implementation. For example, analyses were done for the screening of specific age groups (in particular, >50 years and >60 years). Additionally, the post hoc analyses were conducted on subjects with a UAE >30 mg/d and those with a UAE >50 mg/d, using the specific costs of identifying 1 person with a UAE above these thresholds. Differences in the results of the sensitivity and baseline analyses were related to the effectiveness of fosinopril in

the various subgroups and the costs required to identify 1 person eligible for fosinopril treatment.

RESULTS

The primary end point in the PREVEND-IT trial occurred 17 times in the fosinopril group (16 men, 1 woman) and 28 times in the placebo group (20 men, 8 women) (Figure-1, Table-1).

Costs

In the baseline analysis, the costs of CVEs calculated from the clinical trial were €207 and €148 per subject in the fosinopril and placebo groups, respectively (Table-4). Although fewer events occurred in the fosinopril group, per-person costs in that group were higher due to more costly treatments per event (more percutaneous transluminal coronary angioplasty and coronary artery bypass grafting procedures were performed in this group) (Table-I). However, differences in the costs of CVEs between the 2 groups were not statistically significant. The costs of research were excluded from this analysis.

***Table-4**. Estimated mean costs per person for 2 strategies: screening for albuminuria and treating with fosinopril compared with no screening.*

Cost Component	Estimated Mean Costs (2002 €)		
	Screen and Treat	No Screening	Incremental
Cardiovascular events	207	148	59
Procedures	113	68	45
Hospital contacts	93	80	14
Intervention	1296	0	1296
Fosinopril	1002	0	1002
GP and pharmacist fees	295	0	295
Screening*	385	0	385
Total costs			
Undiscounted	1888	148	1740
Discounted	1808	139	1670

GP = general practitioner.

* Costs of identifying 1 person with albuminuria in the baseline analysis.

The calculated costs were applied to the screen-and-treat and no-screening strategies (Table-4). Adding the estimated costs of €207 for cardiovascular events and €1296 for fosinopril treatment (including GP and pharmacist costs) and screening costs of €385 (36% for prescreening and 64% screening) resulted in estimated costs of €1888 per person (€1808 if discounted). No further screening or treatment costs were considered for the no-screening option, resulting in a total cost of €148 per person (€139 if discounted) (Table-4). Therefore, the difference in discounted costs between the screen-and-treat approach and the no-screening approach was estimated at €1670 per person.

Baseline Cost-Effectiveness Analysis

The higher CVE rate in the placebo group compared with the fosinopril group (6.5% *vs* 3.9%, respectively) translated into an estimated mean number of 0.28 discounted life-years lost per person not using fosinopril, compared with 0.18 years in those receiving fosinopril. These figures were applied to the no-screening and screen-and-treat options, with the result that screen-and-treat was estimated to result in 0.10 LYG per person in the baseline analysis (slightly >1 month).

In the baseline analysis, estimated mean cost-effectiveness was €16,700 per LYG. Figure-2 shows the corresponding scatter plots for the 10,000 bootstrap replicates of net cost and effect in the cost-effectiveness plane, the estimated mean, and the 95% CI. Results are spread across the first and fourth quadrant of the cost-effectiveness plane. The estimated cost-effectiveness was below the informal Dutch threshold of €20,000 per LYG.

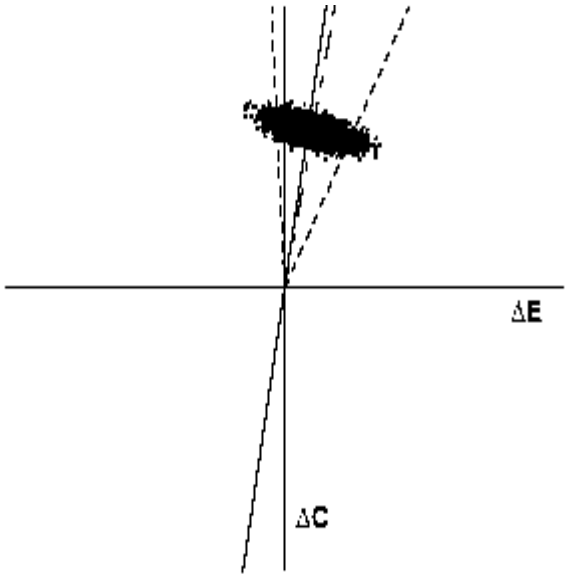
Additionally, we determined the probability that the CER would be above or below various thresholds for maximum willingness to pay for 1 LYG (Figure-3). For 50% of the bootstrap replicates in the baseline analysis, estimated cost-effectiveness was below €16,500/LYG. For a maximum acceptable cost-effectiveness of €20,000, the probability of the screen-and-treat option being cost-effective was estimated at 59% (Figure-3, Table-5).

Sensitivity Analysis

In the sensitivity analysis, we analyzed the cost-effectiveness of limiting treatment to only those subjects with a UAE >30 mg/d or >50 mg/d (Figures-2 and 3, Table-5). Estimated median CERs for those subjects were lower compared with the baseline analysis (€ 12000, €7000 and €16500 for UAE >30, UAE >50 and baseline, respectively), and threshold probabilities increased to >90% for UAE >50 mg/d. Furthermore, the estimated median cost-effectiveness was lower for screening and

treating subjects aged >50 years and >60 years compared with screening all subjects in the baseline analysis.

(2A)



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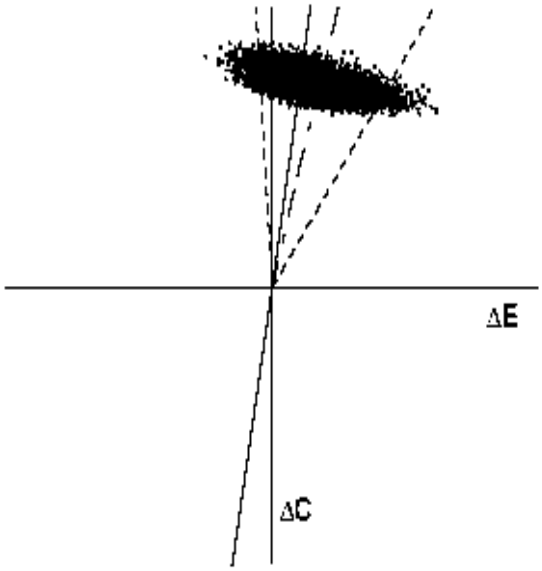

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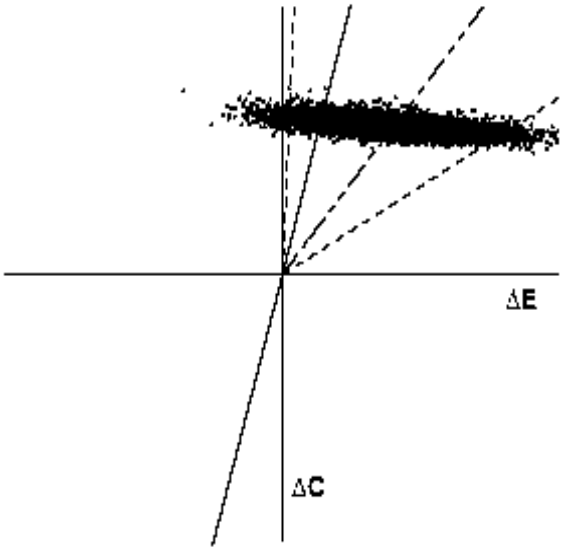


Figure-2. *Cost-effectiveness of screening for albuminuria and subsequent fosinopril treatment compared with no screening (2A) in all subjects with microalbuminuria (urinary albumin excretion [UAE] >15 mg.d (cost effectiveness ratio [CER] = €16,700/life-year gained [LYG]) and in sensitivity analyses in (2B) subjects with UAE>30 mg/d (CER = €12,000/LYG and (2C) subjects with UAE>50 mg/d (CER = €6900/LYG). Scatter-plot represent 10,000 replicates per analysis using bootstrap method. Any cost-effectiveness plane contains net costs in euros (ΔC) on the x-axis and LYG as effects (ΔE) on the y-axis. Dotted lines are 95% CI, the dashed line is the estimated mean, and the solid line is the informal Dutch pharmacoeconomic threshold (€20,000/LYG).*

Table-5. Median cost-effectiveness ratio (CER) and the probability of acceptable cost-effectiveness given a threshold of €20,000 per life-year gained in the baseline and sensitivity analyses.

Analytic Group	Median Cost-effectiveness Ratio (€)	Probability of Acceptable Cost-Effectiveness
All subjects (baseline)	16,500	0.59
▪ UAE >30 mg/d	12,000	0.72
▪ UAE >50 mg/d	7000	0.91
Subjects aged >50 y	13,600	0.63
Subjects aged >60 y	6300	0.80

CER = cost effectiveness ratio, UAE = urinary albumin excretion

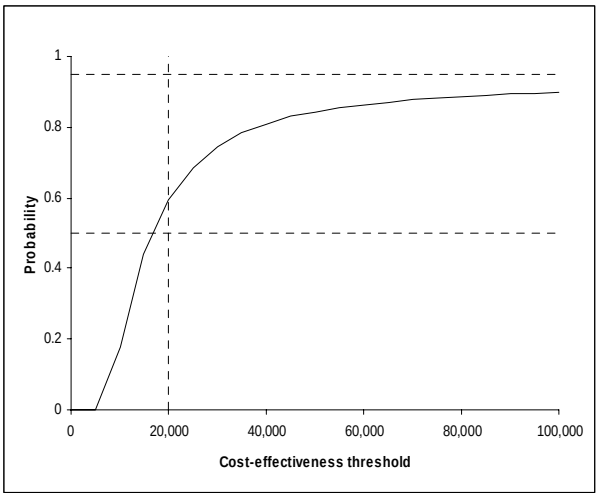
DISCUSSION

This study analyzed the cost-effectiveness of using fosinopril for the primary prevention of CVEs in subjects with albuminuria (UAE >15 mg/d) from the Dutch health care perspective. We estimated a CER for screening and subsequent fosinopril treatment (*vs* placebo) of €16,700/LYG. With a maximum acceptable cost-effectiveness for the Netherlands of €20,000/LYG, our point estimate would be considered cost-effective. Analysis indicated an estimated 59% probability of the screen-and-treat strategy being cost-effective. Although this percentage was not statistically significant for favorable cost-effectiveness, screening for albuminuria and subsequent fosinopril treatment appears to be worth consideration from a pharmacoeconomic perspective. It should be remembered that our study was designed to be hypothesis generating, and our results require further investigation and confirmation.

In sensitivity analyses, we investigated how the cost-effectiveness varied by subgroup. In particular, in subjects aged >50 years and >60 years, a relatively more favorable cost-effectiveness was estimated for a UAE cutoff of >15 mg/d. Also, limiting treatment to those subjects with a UAE >30 mg/d or >50 mg/d was associated with improved cost-effectiveness.

Our study did not explicitly include assumptions about the specificity and sensitivity of the testing sequence during screening (1 UAC measurement and two 24-hour UAE measurements), although testing performance is implicitly incorporated in the analysis. Prescreening through measurement of UAC in a spot morning urine sample is satisfactorily predictive of the UAE (specificity 85%).

(3A)



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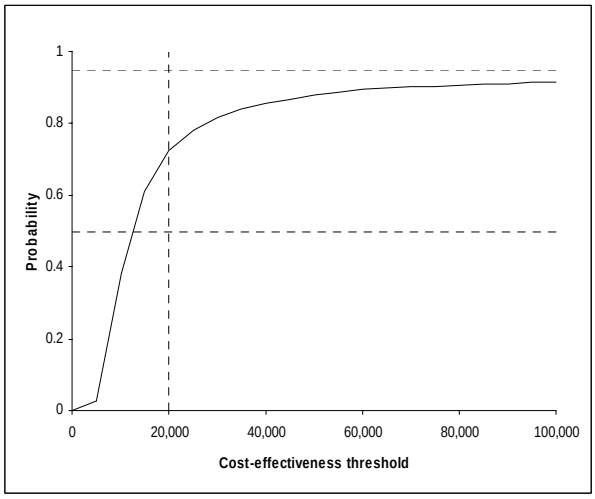

(3C)

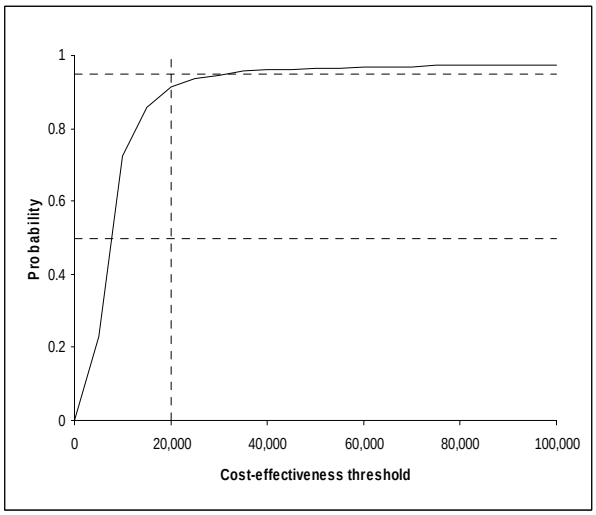

Figure-3*. Cost-effectiveness acceptability curve for screening for albuminuria and subsequent fosinopril treatment compared with no screening (3A) in all subjects (baseline) and in sensitivity analyses in (3B) subjects with urinary albumin excretion (UAE) >30 mg/d and (3C) subjects with UAE>50 mg/d. Any curve represents the probability of screen-and-treat approach being acceptable over a range of cost-effectiveness thresholds for decision makers' willingness to pay. The broken line on the x-axis indicates the cost-effectiveness ratio of €20,000/life-year gained (informal Dutch pharmacoeconomic threshold), and the broken lines on the y-axis indicates 50% and 95% of probability of acceptance*

Some subjects with elevated albumin levels were missed (estimated sensitivity 85%), but prescreening kept the burden and costs of population screening as low as possible [44]. If a better screening procedure were to become available, the costs of identifying 1 person with a UAE above a certain threshold would be lower and would probably result in a more favorable cost-effectiveness outcome.

Only one study comparable to ours was found in the literature (PubMed; up to 2005; key words: cost(-)effectiveness, albuminuria, general population). Boulware *et al* [23] investigated initial dipstick screening for proteinuria in a general population, with follow-up tests to confirm proteinuria and initiate ACE-inhibitor treatment. Their method of screening for proteinuria yielded fewer subjects than

our method of screening for albuminuria, which explains their higher CERs ($53,370–$282,800/QALY gained). In particular, because the prevalence of proteinuria was <1%, their approach required screening of many individuals to identify 1 case. In the PREVEND data [25,26], we found a prevalence of proteinuria of 1.1%, similar to that in the study by Boulware *et al.* However, the prevalence of a UAE >15 mg/d was 12.1% [26] on which our current economic study is based. There were also differences between our and Boulware's approaches in relation to health care systems and specific implementations (GP-screening-based vs population-screening-based) [45] (reference 45 give more detailed about the difference between our and Boulware study). Most important, Boulware *et al* took into account only those savings that applied to the prevention of death from all causes and end-stage renal disease, whereas we focused on the effect of ACE inhibition in preventing CVEs. Inclusion of fosinopril treatment for subjects with overt proteinuria on screening instead of those with a UAE between 15 and 300 mg/d would further improve the cost-effectiveness of screening, given the favorable cost-effectiveness of ACE-inhibitor therapy seen in subjects with proteinuria [46].

Cost-effectiveness of ACE-inhibitor therapy in nonproteinuric populations has been studied previously. Björholt *et al* [17] conducted a substudy of Swedish participants in the HOPE trial to estimate the cost-effectiveness of ramipril treatment for subjects with CVD or diabetes. Their findings indicated net costs of €1940 to €5300/LYG. That estimate included treatment only; costs of screening were not considered. Based on our data, we estimated the cost-effectiveness of fosinopril treatment in subjects with albuminuria at €12,700/LYG (from the baseline analysis).

The PREVEND-IT study was directed at otherwise healthy people (no subjects with diabetes, high cholesterol levels, or high blood pressure); therefore, concomitant drug use was expected to be relatively low and was not considered in the study.

The strength of our study is that it combines population-based data on the prevalence of albuminuria with outcomes of treatment in a subsection of that population. Also, the study was based on documented events occurring during follow-up of the PREVEND-IT study, minimizing the number of assumptions required to perform the entire analysis. The inherent limitation of our study is that it lacks data beyond the specified end points, such as nursing home care for stroke, rehabilitation after acute events, and potential rehospitalizations, with the corresponding costs (lifetime costs of events were not taken into account in our analyses). Therefore, the cost-effectiveness may be even more favorable. However, given the limited period of follow-up in the PREVEND-IT study, lifetime health

gains were modeled using Dutch data on remaining life expectancy and the Framingham life tables.

A major drawback to the PREVEND-IT study was that the apparent difference between lowering UAE and the incidence of CVEs was not statistically significant, possibly because of the limited number of subjects included. But, if the PREVEND-IT study, which was performed on an intention-to-treat basis, were instead performed on per-protocol basis, the relationship between UAE and CVEs might be statistically significant. The per-protocol analysis itself can be provided on request. A larger sample size with longer follow-up (resulting in more events) might have resulted in a statistically significant difference. Finally, this study was limited to a 1-time screening program; inclusion of subsequent screening(s) might result in less favorable cost-effectiveness. In general, cost-effectiveness analysis based on clinical trials has its limitations; in particular, the clinical trial does not reflect the real world, and the time frame is limited.

Further work using our approach should involve the combination of a CVE and the progression of renal disease. For that purpose, a Markov model could be developed with stages corresponding to albuminuria levels, which would offer the opportunity to simulate a periodic screening procedure in the general population. Such models have been developed with a focus on renal disease in subjects with diabetes [20,47], but they have not formally included CV risks. Also, such a Markov model would allow an investigation of cost-effectiveness that included subsequent screening(s) and long-term CV and renal outcomes.

The PREVEND and PREVEND-IT studies were performed in a predominantly white population (>95% of subjects). This may theoretically limit the external validity of our analysis. However, in nonwhites subjects, the prevalence of microalbuminuria, as well as the incidence of CVD, has been shown to be substantially higher than in white subjects [48–51] . We believe that screening for albuminuria and subsequent treatment with an ACE-inhibitor may be more cost-effective in populations with larger proportions of black individuals. In our study, we did not include the cost of complications of fosinopril treatment. Adverse events (particularly cough) were reported by 3.5% of subjects (n=29) in PREVEND-IT [23]. As these adverse events were mild, they did not influence our cost-effectiveness estimate. The possibility of these complications leading to noncompliance was included in our study design.

CONCLUSIONS

This analysis from a Dutch health care perspective suggests the potential favorable cost-effectiveness of a screening program for albuminuria in the general population. The estimated cost-effectiveness of approximately €7000/LYG for subjects with a UAE >50 mg/d was below the Dutch threshold for cost-effectiveness. Cost-effectiveness might be further improved by limiting screening to predefined subgroups (eg, by age, by limiting treatment to those with higher albuminuria levels). Further research is needed to evaluate our findings in other settings using a longer time horizon, including periodically repeated screening and lifetime cost estimates.

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CHAPTER-8

Summary and General Discussion

The first objective of this thesis was to explore the pharmaco-epidemiological aspects of screening on albuminuria in the general population. For this purpose, baseline clinical data and 4.2 years follow-up data of the PREVEND cohort study were used. This clinical data were linked to the electronic pharmacy data from the Inter-Action Data-Base (IADB) which contains the drug-dispensing data from community pharmacies [1]. Firstly, we investigated the effect of a population-based screening (as a determining factor) on the drug use. Secondly, we studied the risk-benefit of specific drugs on cardio-renal risk factors (outcome of drug usage). In this respect we evaluated the long-term effect of statins and hormonal contraceptives on progression or regression of urinary albumin excretion and renal function.

The second objective of this thesis was to explore the pharmaco-economic aspects of a population-based screening on albuminuria. Firstly, we studied the quality requirements for such an analysis through investigating the national pharmaco-economic guidelines; in particular, we reviewed peer-reviewed Dutch health-economic studies with respect to adherence to pharmacoeconomic guidelines. Next, and applying these guidelines we used the data of the PREVEND Intervention Trial and extrapolated the results of this RCT into a lifetime analysis by using models for the cost-effectiveness of screening on microalbuminuria. We investigated whether it is economically worthwhile to implement screening for albuminuria in the general population.

Screening for cardio-renal risk factors : the determinant of drug use

A population based screening is only effective if treatment will be started following the identification of subjects without treatment whereas treatment would be appropriate [2]. In the PREVEND study, a letter intervention was applied with the goal to obtain a higher proportion of patients receiving treatment. The letter contained the result of screening: actual blood pressure and cholesterol level as well as the presence of an abnormal plasma glucose and UAE. The letter was sent to both the participant and her / his general practitioner (GP). The letter adviced the GP on initiating, either a blood pressure (BPLD) and / or lipid lowering drug (LLD).

In ***chapter 2***, we evaluated the effect of this letter intervention on prescribing of BPLD and / or LLD. A year after screening, our therapeutic advice was followed in about one of three subjects with hypertension and one of four subjects with hyperlipidemia. We found that the GP's decision to follow our advice was influenced by the level of the risk factor itself, but not by the presence of other cardiovascular risk factors.

Another aspect of a population-based screening program is that it might be possible that some participants experience harm [3-4]. The assumption is that the benefits of early diagnosis in asymptomatic individuals will outweigh any possible 'side-effect' associated with screening, diagnosis and treatment. Some argue against a screening because such programs may result in medicalisation. However, little is known yet about negative consequences of a screening program for cardiovascular and renal risk factors in early prevention.

In ***chapter* 3**, we studied the effect of population-based screening for cardio-renal risk factors on drug prescribing. We found that incidence of prescribed drugs, either related or un-related to the screening purpose, was not different between those who participated and those who did not participate in the PREVEND screening. Thus, our data showed that a screening program to improve cardiovascular and renal conditions does not lead to higher drug use in the screened population compared with the unscreened population. This study also showed that a targeted screening, that is screening in a cohort that is likely to be at higher risk, enhances appropriate drug use; i.e. drug use increases in the drug classes expected and not overall.

Cardio-renal risks factors: the outcome of drug use

Many drugs are found to be related to urinary albumin excretion (UAE). In the second section of the pharmacoepidemiological part of this thesis, two drug classes were investigated in this respect; hormonal contraceptives (HC) and lipid lowering drugs (statins). In ***chapter 5***, we considered in detail the impact of long-term use of HC on changes in blood pressure (BP), UAE and glomerular filtration rate (GFR). We found that the start of HC was associated with worsening of BP, UAE and GFR. Our data also showed that cessation of HC resulted in an improvement of those outcomes. With respect to the generation of HC, our data suggest that third generation agents might be more harmful than second generation HC. These data suggest that long-term HC use may worsen cardiovascular and renal conditions, but stopping HC restores such conditions.

In ***chapter 4*** we investigated the effect of statins on UAE and GFR, using the data from the randomised controlled trial PREVEND-IT and the observational PREVEND cohort. In the PREVEND-IT we found no effect after 4 year treatment of 40 mg pravastatin on UAE. In contrast, our observational PREVEND cohort study of 3440 subjects showed that statins induced a rise in UAE, especially when used in higher dose and for longer duration. From both studies, we could not confirm that

statins are associated with better GFR preservation. On the other hand we also did not find a negative effect on GFR.

Screening for albuminuria : the pharmaco-economic aspect

It has been shown that albuminuria may predict cardiovascular disease and renal function outcome in subjects with diabetes [5-7] or hypertension [8-13] as well as in the general population [14-20]. Therefore, micro-albuminuria might be an easy detectable marker for vascular dysfunction. In that respect, screening on albuminuria may be a useful tool to identify subjects at risk for CVD and/or progressive renal failure [21-22] .

However, before screening programs can be implemented, cost effectiveness of the program needs to be established. In ***chapter 7***, we estimated the cost-effectiveness of screening on albuminuria and subsequent treatment with fosinopril of subjects with UAE > 15 mg/d for early prevention of cardiovascular and renal morbidity and mortality. The data from PREVEND-IT, a double blind RCT using a 2x2 factorial design was extrapolated into a lifetime analysis. The estimated costs of screening were derived from the PREVEND observational study. Our study was designed as far as possible according to the Dutch guidelines for pharmacoeconomic research (*chapter 6*); for that purpose, pharmacoeconomic guidelines were investigated in detail by comparing them with published health-economic studies.

Our estimation of the cost-effectiveness ratio (CER) from the Dutch health care perspective was € 16,700/life year gained (LYG). With maximum acceptable cost-effectiveness willingness to pay for the Netherlands of € 20,000/LYG, our point estimate would be considered cost-effective. Stocahstic analysis indicated an estimated 60% probability of this screening and treatment being cost-effective. Limiting the screening and treatment to subjects over 60 years old and subjects with UAE > 50 mg/d improves cost-effectiveness. Because this study was based on the non-significant trend toward fewer CV events with fosinopril in PREVEND-IT, the result of this study should be interpreted as a hypothesis-generating study and these findings need confirmation in a larger multi-center study. In this study, we as expected had no case of end stage renal disease (ESRD) during the 4 years follow-up, thus the endpoints of PREVEND-IT were only for cardiovascular events in the end. We also did not include follow-up costs of the events; its inclusion would have enhanced cost-effectiveness further

Pharmacoepidemiologic and pharmacoeconomics : the aspect of drug use

All studies in this thesis provide insight into aspects of drug use and drug prescribing Combining clinical data of the PREVEND observational cohort and the PREVEND-Intervention Trial with drug-dispensing data of IADB has resulted in an dataset which allows us to do drug utilization research and pharmaco-epidemiologic and pharmaco-economic studies. Below, we review the chapters in this thesis with regard to the availability of this unique set of drug use data.

Firstly, we focused on determinants of the drug use. We investigated whether a population-based screening (as a determinant) could influence drug prescripton (*chapter 3*). We demonstrated that a screening program itself does not lead to more drug prescribing, neither in the screening-related nor in the screening -unrelated drugs. Comparing the patterns of drug use of the screened enriched population, ascreened random sample and an un-screened population increased our understanding how and when drugs are prescribed in these different groups. We estimated the number of patients exposed to drugs within a given time period. Such estimates gave us insight in the prevalence of drug use at the time of the initial screening as well as on the incidence of use of drugs in selected time periods.

Drug utilization research may enable us to assess whether an intervention undertaken to improve drug use by giving a treatment recommendation to the general practitioner has the desired impact on drug prescribing. In *chapter 2*, we have shown that an intervention, such as a letter recommendation, significantly changed prescribers' attitude to make a therapeutic decision for their patient. We have shown that the subjects / patients characteristics (e.g. demographic parameters, cardio-renal risk factors and comorbidity) are also playing a role in profiles and trends in drug use.

Pharmacoepidemiology focuses on the benefits and adverse-effects of drugs in the general population. The driving force behind this development was a growing awareness that health outcomes of drug use in the rigorous setting of randomized clinical trials is not necessarily the same as health outcome of drug use in everyday practice. The clinical trials often have limited samples of carefully selected patients. Moreover, drug utilization research also provides insight into the efficiency of drug use, i.e. whether a certain drug therapy provides relevant health gains. Drug utilization research can thus help to set priorities for the rational allocation of health care budgets. Therefore for the second aspect of drug use, we focused on health outcome (benefits and side-effects) and economic consequences of drug use (*chapter 4, 5 and 7*). In these chapters, we assessed the potential effects of a specific drug (as an exposure factor) on cardio-renal outcomes such as changes

in blood pressure, UAE and GFR. Economic consequences including cost / benefit of treatment were estimated using the data from a clinical trial (*chapter-7*)), using state-of-the-art pharmacoeconomic methods.

Thirdly, we provided detailed information on patterns of drug use, particularly for those drug related to cardio-renal outcomes, as we were interested in the differences between the effects of current versus former users. Such descriptions are most meaningful when they are part of a continuous evaluation system, i.e. when the patterns are followed over time and trends in drug use can be described, enabling us to specify the differences between those who have stopped, started or continuously used a medication (chapter 4 and 5).

Fourthly, we could assess the quality of drug use. Quality indicators of drug use that are included in our analysis involve type of regimens, drug dosage and period of drug exposure. In this thesis, these indicators are used to determine the difference between type of regimen, drug dosage and period of expousre on renal outcomes such as UAE and GFR.

Methodological consideration: experiences and challenges

Study design, confounding and propensity score in observational study

An important aspect of our studies is that we were able to provide a data from a prospective observational cohort study with long term follow-up (4.2 years for the clinical data of PREVEND and 6.5 years of pharmacy data of IADB). Observational studies always raise concerns about biases in some that may account for or contribute to the findings. In observational studies, patients and their physicians select treatment on the basis of clinical need or preference, which can result in differences in clinical outcomes solely because of differences between those who do and do not receive treatment (indication bias). In contrast, random assignments in an RCT garantees that patient characteristics, both known and unknown, will be the same in the treatment groups. However, knowledge derived from RCT's cannot always be translated directly to daily clinical practice. Patients that are included in an RCT frequently are not the ones that clinicians encounter in their office. This is especially true for nephrology, as in many of the important cardiovascular trials studying the effect of antihypertensives, statins, or anticoagulants patients with chronic kidney disease are excluded. In other words, the observational study provides information about treatment in the population in daily practice, and differs from the situation in clinical trials [23-24] .

An alternative way of dealing with confounding by indication caused by non-randomized assignment of treatments in cohort studies, is the use of

propensity scores, a method developed by Rosenbaum and Rubin [25-26]. The propensity score of an individual is defined as the conditional probability of being treated given the individual's co-variates. However, this technique can not adjust for residual un-measured covariates, but can aid in understanding determinants of drug use and lead to improved estimates of drug effects [27].

Internal and external validity-All studies in the pharmacoepidemiology part of this thesis are based on electronic-drug-dispensing data from community pharmacies. We used the computerised pharmacy database (from IADB) that provides valid and reliable information on drug use. Previous studies have demonstrated that dispensing data from Dutch pharmacies offer an accurate picture of the use of prescription drugs outside the hospital [28-29] . However, one limitation is that pharmacy data do not have information about indication of the drug.

Use of large computerised databases and record linkage has become increasingly important in pharmacoepidemiology research. The greatest advantages of using routinely collected data are minimisation of study costs and time required to complete a study, considerations that are particularly relevant for longitudinal studies such as in this thesis. The advantage of using databases also includes the possibility of obtaining large sample sizes and reduces the risk for recall bias, which is a significant problem in interviews and questionnaire methods. Another advantage of using pharmacy data is the detailed information regarding drug use (duration, dose, and drug classes) during the whole study period. We also were able to compare the drug use between subjects in the PREVEND cohort with drug use in the general population (from IADB).

Clinical impact and future research

A screening programme on microalbuminuria could also help to detect subjects with undiagnosed diabetes, hypertension and hyperlipidemia. Our study showed that one third of the hypertensive subjects were not yet known to have hypertension and one third of those with hypertension were not adequately treated. Comparable data were found for hyperlipidemia. Furthermore, we found that the likelihood to use blood pressure or lipid lowering drugs increased when higher values of blood pressure or cholesterol level were found. Unfortunately, the presence of concomitant risk factors did not influence the prescribing behaviour. This aspect was further studied in chapter-3. After a long period of follow-up, we could not find any medicalization effect in our screened population compared to a

non-screened population. We could thus not confirm that screening for cardio-renal risk factors leads to more drug prescribing and might therefore be harmful for the population. Interestingly, we also showed that a screening is in fact only effective in improving drug use, when it is limited to those with a higher risk, such as in a cohort enriched for albuminuria.

Another point addressed in this thesis refers to the relation between use of a specific drug and the change in albuminuria and renal function over time. Firstly, we should pay attention to our finding that statins are associated with a rise in albuminuria in our observational study. Although this finding was not confirmed in our PREVEND IT clinical trial, this finding requires further attention. Fortunately, statins were not associated with a fall in GFR. Secondly, we found that hormonal contraceptives independently were associated with a worsening of blood pressure, albuminuria and renal function, but our data also showed that stopping may result in correction of these effects. Even though our data are limited to subjects with only modest renal damage, we do think these data are of interest for clinicians as also early renal damage is associated with an impaired renal and vascular prognosis. Because statins and hormonal contraceptives are widely used in the general population our results may be of public health importance and need confirmation in other studies.

Can we implement a screening program for albuminuria in daily practice? The evidence showed that a screening program with subsequent treatment for those with an elevated albuminuria improved CV morbidity and mortality. Our data suggest that screening of albuminuria and subsequent treatment with an ACE inhibitor appeared to be cost effective in our population. The costs needed to gain one life year were € 16,700. The costs were even lower when we limited the analysis to subjects with an UAE > 50 mg/d and an age over 50 or 60 year. This study is based on a single screening for microalbuminuria of the general population. Further studies are needed to evaluate whether re-screening at some later time offers additional benefit. A Markov Model should be developed to simulate a periodic screening procedure in the general population inclusive long-term beneficial effects on renal damage.

The PREVEND cohort and IADB form a unique set of data. Presently, third screening of the PREVEND subjects has been completed and data on cardiovascular and renal morbidity and mortality are available and pharmacy data havebeen collected until the end of 2005. These long-term follow-up (approximately 10 years) makes it possible to provide longitudinal analyses on cardiovascular and renal disease progression in relation to drug use.

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Samenvatting (Summary in Dutch)

De eerste doelstelling van dit proefschrift was het onderzoeken van de farmaco-epidemiologische aspecten van bevolkingsonderzoek op albuminurie. Hiervoor is gebruik gemaakt van klinische gegevens uit de PREVEND-cohortstudie (eerste screening en vervolggegevens over 4,2 jaar). Deze klinische gegevens werden gekoppeld aan de elektronische apotheekgegevens van de InterActie DataBank (IADB), die gegevens bevat over geneesmiddelenuitgifte door de apotheken. Eerst hebben we het effect van bevolkingonderzoek (als determinant) op geneesmiddelgebruik onderzocht. Vervolgens bestudeerden we de risico's en baten van specifieke geneesmiddelen op cardiovasculaire en renale risicofactoren (als uitkomst van geneesmiddelen-gebruik). We evalueerden daarbij het langetermijn effect van statines (cholesterolverlagers) en hormonale anticonceptiva op progressie en regressie in urine albumine uitscheiding en nierfunctie.

De tweede doelstelling van dit proefschrift heeft betrekking op de farmaco-economische aspecten van bevolkingsonderzoek op albuminurie. Eerst bestudeerden we de kwaliteitseisen voor een dergelijke analyse zoals vastgelegd in nationale farmaco-economische richtlijnen en bekeken we in hoeverre deze richtlijnen voor het uitvoeren van farmaco-economische studies worden nageleefd. Vervolgens gebruikten we de gegevens van de PREVEND Intervention Trial (IT), die op basis van modellen voor het berekenen van de kosteneffectiviteit van screening op albuminurie, geëxtrapoleerd werden naar de 'lifetime' analyse. We onderzochten of het kosteneffectief zou zijn om de algemene bevolking op albuminurie te screenen.

Bevolkingsonderzoek naar cardiovasculaire en renale risicofactoren : de determinant van geneesmiddelengebruik

Bevolkingonderzoek is alleen effectief als daarna behandeling wordt begonnen van hen die nog geen behandeling hadden maar die wel zouden moeten hebben. Binnen de PREVEND-studie werd een brief-interventie toegepast om zodoende een groter proportie aantal patiënten te kunnen behandelen. De brief bevatte de screeningsresultaten: gemeten bloeddruk en cholesterolwaarde alsook de aanwezigheid van abnormale plasma-glucose en urine-albumine excretie. De brief werd verzonden naar de deelnemer van PREVEND en naar hun huisarts. De brief gaf advies aan de huisarts omtrent het gebruik van bloekddruk- en/of lipideverlagende geneesmiddelen.

In hoofdstuk 2 evalueren we het effect van deze brief-interventie op het voorschrijven van bloeddruk- en/of lipideverlagende geneesmiddelen. Een jaar na de eerste screening werd het therapeutische advies slechts opgevolgd bij één op de drie personen met hypertensie en één op de vier personen met hyperlipidemie. Wij stelden vast dat het besluit van de huisartsen om ons advies al dan niet op te volgen beïnvloed werd door het niveau van de risicofactor zelf en niet door de aanwezigheid van andere cardiovasculaire risicofactoren.

Een ander aspect van een populatiescreeningsprogramma is dat participanten mogelijkerwijs negatieve effecten ondervinden. We veronderstellen dat de baten van vroege diagnostisering bij asymptomatische individuen opwegen tegen de mogelijk aan screening, diagnostisering en behandeling gerelateerde bijwerkingen. Een argument tegen screeningsprogramma's zou kunnen zijn dat deze programma's kunnen resulteren in medicalisering. Echter, over negatieve consequenties van screeningsprogramma's op cardiovasculaire en renale risicofactoren, is tot op heden nog maar weinig bekend.

In hoofdstuk 3 hebben we het effect van een bevolkingsonderzoek op cardiovasculaire en renale risicofactoren op het voorschrijven van geneesmiddelen onderzocht. We stelden vast dat de incidentie van voorschrijven van aan de screening gerelateerde en niet aan de screening gerelateerde geneesmiddelen niet verschilde tussen hen die wel en hen die niet aan PREVEND deelnamen. Kortom, de data lieten zien dat een screeningsprogramma ter verbetering van cardiovasculaire en renale conditie, niet leidt tot een toename in het gebruik van geneesmiddelen. Onze studie laat eveneens zien dat toegespitste screening in een cohort met een hoger risicoprofiel, leidt tot een toename van geneesmiddelen die gerelateerd zijn aan het preventiedoel van de screening en niet van andere geneesmiddelen.

Cardiovasculaire en renale risicofactoren : de resultaten van geneesmiddelengebruik

Veel geneesmiddelen worden in verband gebracht met urine-albumine excretie. Als tweede onderdeel van de farmaco-epidemiologische aspecten in dit proefschrift, werden twee geneesmiddelgroepen onderzocht; hormonale anticonceptiva en lipideverlagende middelen (statines). In hoofdstuk 5 hebben we de langetermijn invloed van hormonale anticonceptiva op veranderingen in bloeddruk, urine-albumine excretie en nierfunctie (in termen van glomerulaire filtratiesnelheid), onder de loep genomen. De start van hormonale anticonceptiva bleek geassocieerd te zijn met een verslechtering in de bloeddruk, urine-albumine

excretie en nierfunctie. De data toonden eveneens verbetering in de 2e uitkomsten na het stoppen van hormonale anticonceptiva. Derde generatie hormonale anticonceptiva bleken van grotere invloed op de veranderingen in de uitkomsten dan tweede generatie hormonale anticonceptiva. Resumerend indiceren onze data dat hormonale anticonceptiva een negatief effect hebben op cardiovasculaire en renale uitkomsten, terwijl het stoppen van deze hormonale anticonceptiva mogelijkerwijs weer leidt tot normale uitkomstwaarden.

In hoofdstuk 4 hebben we het effect van statines op urine-albumine concentratie en nierfunctie bepaald op basis van data uit de gerandomiseerde PREVEND-IT-studie en de observationele PREVEND-studie. Na vier jaar vonden we op basis van de PREVEND-IT-gegevens voor pravastatine (40 mg) geen effect op urine-albumine excretie. Daarentegen bleek uit het 3440 individuen tellende PREVEND-cohort, dat statines resulteren in een verhoging van de urine-albumine excretie. Dit bleek met name het geval bij hogere doseringen en bij individuen die statines reeds voor een langere tijd ontvingen. Op basis van zowel de PREVEND-IT als de PREVEND-studie, kunnen we niet bevestigen dat statines geassocieerd zijn met een betere nierfunctie. We vonden echter ook geen verslechtering van de nierfunctie.

Screening op albuminurie : het farmaco-economische aspect

Er is aangetoond dat albuminurie het optreden van cardiovasculaire en renale aandoeningen kan voorspellen bij zowel mensen met diabetes als in de algemene bevolking. Daarom lijkt microalbuminurie een makkelijk detecteerbare voorspeller te zijn voor vasculaire dysfunctie. In lijn hiermee lijkt screenen op albuminurie dan ook een nuttige methode om mensen met een verhoogd risico op het ontwikkelen van cardiovasculaire en renale aandoeningen op te sporen.

Vóór screeningsprogramma's worden geïmplementeerd, dient de kosteneffectiviteit ervan te zijn berekend. In hoofdstuk 7 is een schatting gemaakt van de kosteneffectiviteit van screenen op albuminurie en behandeling met fosinopril bij een urine-albumine excretie ≥ 15 mg/d voor de preventie van cardiovasculaire en renale morbiditeit en mortaliteit. De gegevens van PREVEND-IT op basis van een 2x2 factorial design, werden geëxtrapoleerd naar een 'lifetime' analyse. De kosten voor screenen werden geschat op basis van gegevens uit de observationele PREVEND-studie.

In hoofdstuk 7 hebben we de kosteneffectiviteit van een screeningsprogramma geschat op € 16.700 per gewonnen levensjaar. De analyse is gedaan vanuit het gezondheidszorgperspectief. Volgens de huidige Nederlandse

richtlijnen voor farmaco-economische studies ligt de maximale 'willingness to pay' op € 20.000 per gewonnen levensjaar en zou de geëvalueerde screeningsprocedure als kosteneffectief beschouwd mogen worden. De analyse leidde tot een schatting met een aannemelijkheid van 60% dat een soortgelijk screeningsprogramma bij de huidige afkappunt van € 20.000 per gewonnen levensjaar kosten effectief is. Een gunstigere uitkomst voor de kosteneffectiviteit werd gevonden indien de screening en behandeling beperkt zouden blijven tot patiënten ouder dan 60 jaar en patiënten met een urine-albumine excretie > 50 mg/d. In deze studie werden geen 'follow-up' kosten van de opgetreden events meegenomen, die onze resultaten waarschijnlijk positief beïnvloeden. Omdat deze studie gebaseerd werd op een niet-significante trend in de richting van minder cardiovasculaire gebeurtenissen, dienen de resultaten geinterpreteerd te worden als hypothese-genererend. Grotere multi-center trials zijn nodig om onze resultaten te bevestigen.

Klinische betekenis en toekomstig onderzoek

Ons screeningsprogramma kan een bijdrage leveren aan de opsporing van patiënten met ongediagnostiseerde diabetes, hypertensie en hyperlipidemie. Onze studie toonde aan dat van eenderde van de gevonden hypertensieve patiënten nog niet bekend was dat zij aan hypertensie leden en dat eenderde inadequaat behandeld werd. Vergelijkbare data werden gevonden voor patiënten met hyperlipidemie. Verder ontdekten we dat de kans op het gebruik van antihypertensiva of antihyperlipidemia groter was bij respectievelijk een hogere bloeddruk en een hogere cholesterolwaarde. Helaas bleek de aanwezigheid van additionele risicofactoren niet van invloed op het voorschrijfgedrag. Dit aspect is verder onderzocht en beschreven in hoofdstuk 3. Na een lange 'follow-up' studie, waarin een gescreende populatie vergeleken werd met een populatie die niet onder invloed van een dergelijk screeningsprogramma had gestaan, kunnen we geen medicalisatie-effect aantonen. Daarom kunnen we dan ook niet bevestigen dat screenen op cardiovasculaire en renale risicofactoren leidt tot het voorschrijven van meer geneesmiddelen en misschien leidt tot negatieve effecten op populatieniveau. Onze resultaten laten echter wel zien dat screening voornamelijk effectief is in het verbeteren van het geneesmiddelengebruik door de individuen met een hoog risicoprofiel, zoals bijvoorbeeld in een verrijkt cohort van individuen met albuminurie.

Een ander punt dat in dit proefschrift aan de orde komt is de relatie tussen het gebruik van een specifiek geneesmiddel en de veranderingen in urine-albumine excretie en nierfunctie in de tijd. Allereerst moeten we hier aandacht

besteden aan onze bevinding dat statines op basis van onze observationele studie geassocieerd zijn met een verhoging in urine-albumine excretie. Hoewel deze relatie niet bevestigd werd in onze klinische PREVEND-IT studie, vereist deze bevinding nadere aandacht. In de observationele studie werden statines niet geassocieerd met een afname in de nierfunctie. Daarnaast bleken hormonale anticonceptiva onafhankelijk geassocieerd met een verslechtering van de bloeddruk, urine-albumine excretie en nierfunctie; de nadelige effecten zijn echter terug te draaien door te stoppen met het gebruik van deze middelen. Alhoewel onze gegevens slechts individuen met vroege nierschade betreffen, menen wij dat deze data relevant zijn voor clinici. omdat vroege nierschade een slechte cardiovasculair en renale prognose heeft. Omdat homonale anticonceptiva en statines breed toegepast worden in de algemene populatie kunnen onze resultaten van belang zijn voor de volksgezondheid en is bevestiging door andere studies vereist.

Kunnen we een screeningsprogramma met de focus op albuminurie implementeren in de dagelijkse praktijk? Het is al bekend dat een screeningsprogramma gevolgd door behandeling van albuminurie leidt tot verbeterde prognoses wat betreft cardiovasculaire morbiditeit en mortaliteit. Onze bevindingen suggereren ook dat screenen op albuminurie en daaropvolgende behandeling met een ACE-remmer kosteneffectief is in de PREVEND-populatie. De kosten om één levensjaar te winnen, bedragen € 16.700. Deze kosten bleken nog lager uit te vallen in subgroepen met urine-albumine excretie hoger dan 50 mg/d en een leeftijd boven 50 of 60 jaar. Hierbij dient opgemerkt te worden dat de analyse berust op een eenmalige screening. Vervolgstudies zijn nodig om te bepalen of herscreening op een later tijdstip extra voordeel oplevert. Voor dit laatste dient een Markov-model ontwikkeld te worden om een periodieke screeningsprocedure op populatieniveau te kunnen simuleren, inclusief nuttige langetermijneffecten op nierschade.

De PREVEND-cohortstudie en de IADB vormen een unieke dataverzameling. Inmiddels is de derde screening van de PREVEND-studie voltooid en zijn gegevens over cardiovasculaire en renale morbiditeit en mortaliteit beschikbaar en zijn apotheekdata verzameld tot en met het jaar 2005. Deze langetermijn 'follow-up' data (ongeveer 10 jaar) maken het mogelijk om longitudinaal analyses op de progressie in cardiovasculaire en renale ziekten uit te voeren in relatie tot het geneesmiddelengebruik.

Ringkasan (Summary in Bahasa Indonesia)

Bagian pertama dari tesis ini bertujuan untuk meneliti aspek-aspek farmako epidemiologi dari screening albuminuria. Penelitian ini menggunakan data klinis pasien yang berpartisipasi pada dua kali tahapan screening (PREVEND studi). Kedua tahap screening ini berjarak lebih kurang 4,2 tahun. Data klinis ini kemudian bertaut dengan data peresepan obat dari apotik. Data peresepan obat ini tersedia di dalam suatu elektronik database yang disebut Inter-Action Data-Base (IADB). Di dalam tesis ini, kami meneliti apakah suatu program screening bisa menjadi ***kausal*** dari penggunaan obat. Selanjutnya, kami juga meneliti ***dampak/akibat*** dari penggunaan obat terhadap risiko-risiko penyakit jantung dan ginjal. Untuk itu, kami meneliti dampak jangka panjang statins (obat untuk penurun kolesterol darah) dan hormon kontrasepsi pada perubahan kadar albumin urin dan fungsi ginjal.

Pada bagian kedua dari tesis ini, kami menyelidiki aspek-aspek farmako ekonomi dari screening albuminuria di populasi umum. Data yang digunakan kali ini adalah data dari PREVEND Interventon Trial (IT). Hasil dari penelitian ini akan dicoba untuk diterapkan pada masyarakat umum, menggunakan model cost-effectiveness dari screening microalbuminuria. Kami meneliti apakah screening albuminuria pada populasi umum ini *cost-effective*. Selanjutnya, kami juga melakukan review penelitian-penelitian farmako-ekonomi yang telah dilakukan di Belanda, ketaatannya terhadap guideline untuk penelitian di bidang ekonomi kesehatan.

Dampak program screening terhadap penggunaan obat.

Suatu program screening akan efektif apabila upaya-upaya pengobatan dilakukan secara langsung setelah hasil screening diketahui. Pada PREVEND studi, kami menggunakan ‘surat’ sebagai alat intervensi untuk meningkatkan proporsi jumlah pasien yang menerima pengobatan. Di dalam surat tersebut, kami menginformasikan hasil screening dari pasien seperti tingginya tekanan darah pasien, kadar lipid, gula darah, dan kadar albumin di air seni (urin). Surat ini dikirimkan untuk pasien itu sendiri dan dokter yang merawatnya. Di dalam surat ini kami memberi anjuran agar pasien diberikan obat penurun tekanan darah dan / atau obat penurun kolesterol, tentunya hanya untuk pasien yang mempunyai hasil screening yang abnormal.

Pada Bab 2, kami telah mengevaluasi efek dari intervensi ini terhadap peresepan obat-obat antihypertensive dan anti cholesterol. Setahun setelah

screening, ternyata nasihat pengobatan yang kami anjurkan hanya diikuti oleh satu dari tiga penderita hipertensi dan satu dari empat penderita hiper lipidemia. Kami juga menemukan bahwa keputusan para dokter untuk memberikan obat penurun tekanan darah dan kolesterol, dipengaruhi hanya oleh tingginya tekanan darah dan kadar lipid pasien saja. Sedangkan faktor risiko lainnya seperti usia, jenis kelamin, riwayat penyakit jantung, tingginya kadar gula darah dan albumin dalam urin dan faktor risko lainnya, tidak berpengaruh terhadap keputusan dokter dalam pemberian obat.

Disamping itu,. Selain keuntungan karena ditemukannya penyakit secara dini, program screening itu sendiri ternyata dapat memberikan dampak negatif atau efek samping pada pasien, terutama dampak yang berhubungan langsung dengan screening, penegakan diagnosis dan pengobatan yang diberikan. Beberapa kalangan yang menentang program screening berpendapat bahwa program seperti screening ini akan membawa dampak medikalisasi di masyarakat (pemeberian obat secara massal di masyarakat). Namun demikian, efek negatif dari program screening yang ditujukan untuk pencegahan dini penyakit-penyakit jantung dan ginjal, belum banyak diteliti.

Pada Bab 3, kami meneliti efek dari screening terhadap risiko penggunaan obat. Kami menemukan bahwa insidensi penggunaan obat, baik obat yang berhubungan dengan tujuan dari screening ataupun yang tidak berhubungan dengan tujuan screening, tidak berbeda secara bermakna antara pasien yang berpartisipasi dalam screening dengan yang tidak berpartisipasi dalam screening. Studi kami menyimpulkan bahwa screening tidak berakibat terhadap peningkatan penggunaan obat pada populasi screening. Selanjutnya, kami menemukan bahwa jika screening dilakukan hanya pada populasi yang mempunyai risiko tinggi, maka program screening tersebut akan berdampak meningkatkan penggunaan obat khususnya obat-obat untuk penyakit yang berhubungan dengan program screening itu sendiri, dan tidak terhadap penggunaan obat secara umum.

Hubungan antara penggunaan obat dan faktor risiko penyakit cardio-renal

Pada bagian kedua farmakoepidemiologi tesis ini, kami meneliti efek dari hormon kontraseptif dan statin. Penelitian terdahulu menunjukkan efek obat ini terhadap faktor risiko penyakit cardio-renal. Pada Bab 5, kami meneliti hubungan antara penggunaan hormon kontrasepsi dengan peningkatan tekanan darah dan level albumin dalam urin, dan penurunan fungsi ginjal. Studi kami menemukan bahwa penggunaan hormon kontrasepsi akan meningkatkan tekanan darah dan kadar

albumin urin serta penurunan fungsi ginjal. Jika hormon kontrasepsi dihentikan penggunaannya, menyebabkan efek tersebut *reversible*. Penelitian kami juga menemukan bahwa 'generasi ketiga' hormon kontrasepsi mungkin lebih berdampak negatif dibandingkan generasi kedua, terutama pada penyakit jantung dan ginjal, tetapi efeknya akan kembali seperti semula jika berhenti menggunakannya.

Pada Bab 4, kami meneliti efek statin pada kadar albumin urin dan fungsi ginjal. Kami menggunakan data uji klinik PREVEND IT dan data PREVEND observational studi. Data uji klinik menunjukkan tidak ditemukannya peningkatan kadar albumin dalam urin setelah pemberian terapi 40 mg pravastatin selama 4 tahun. Namun sebaliknya, observasional data 3440 pasien menunjukkan adanya peningkatan kadar albumin urin, terutama pada pasien yang menggunakan dosis tinggi dan dalam jangka waktu yang lama. Dari kedua studi tersebut, kami tidak bisa menyimpulkan bahwa penggunaan obat statins berhubungan dengan peningkatan fungsi ginjal pasien, malah sebaliknya kami menemukan efek negatif pada fungsi ginjal.

Aspek farmakoekonomi dari screening albuminuria

Telah banyak diketahui bahwa albuminuria merupakan predictor unutk penyakit jantung dan ginjal, tidak hanya pada pasien diabetes tetapi juga di populasi umum. Sehingga microalbuminuria bisa dijadikan sebagai *marker* yang relevan untuk *vascular dysfunction*. Dengan kata lain, screening albumin di dalam urin dapat digunakan sebagai alat pendeteksi untuk risiko penyakit jantung dan progresifitas penyakit gagal ginjal.

Namun, sebelum program screening bisa diterapkan, perlu dievaluasi terlebih dahulu *cost-efectiveness* dari program screening tersebut. Pada Bab 7, kami telah mengevaluasi *cost-efectiveness* dari screening dan terapi albuminuria sebagai pereventif penyakit jantung dan ginjal. Data yang kami digunakan adalah data uji klinik PREVEND IT dengan 2x2 *factorial design*, Data pembiayaan program screening itu sendiri menggunakan data dari PREVEND observational studi.

Dari perspektif pelayanan kesehatan di Belanda, perkiraan *cost-efectiveness ratio* (CER) untuk program screening and terapi albuminuria ini adalah sebesar 16.700 EUR untuk setiap peningkatan usia harapan hidup (LYG). *Cost-efectiveness ratio* ini masih dibawah maksimum *willingness to pay* di Belanda, yaitu sebesar 20.000 EUR untuk setiap peningkatan usia harapan hidup. Studi ini juga menunjukkan bahwa *cost-efectiveness* program screening dan terapi albuminuria ini adalah sebesar 60% berada di bawah maksimum willingness to pay. *cost-*

efectiveness ratio akan meningkat 80-90% jika screening dan terapi albuminuria dibatasi hanya untuk individu-individu yang berumur lebih dari 60 tahun dan kadar albumin urin lebih dari 50 mg per hari. Studi farmakoekonomi ini didasarkan pada hasil uji klinik PREVEND-IT, dimana hasi penelitian tersebut menunjukkan adanya tren penurunan kejadian penyakit jantung pada individu yang mendapatkan terapi fosinopril, dibandingkan dengan individu yang hanya mendapatkan placebo. Namun hasil uji klinik ini tidak berbeda bermakna secara statistik. Karena itu hasil studi ekonomi ini harus diinterpretasikan sebagai suatu *hipothesis-generating* studi dan perlu konfirmasi penelitian lebih lanjut. Selama 4 tahun periode penelitian, kami tidak ditemukan kasus *end stage renal disease* (ESRD), sehingga endpoint dari PREVEND-IT hanya untuk kasus-kasus penyakit jantung saja. Kekurangan lain dari penelitian ini adalah tidak diikutsertakannya biaya 'follow-up' perawatan pasien diluar ruamh sakit yang mungkin akan mempengaruhi hasil secara bermakna.

Dampak klinis dan penelitian di masa datang

Program screening yang kami lakukan, ternyata mampu mendeteksi kasus-kasus baru untuk diabetes, hipertensi dan hiperlipidemia yang sebelumnya tidak terdiagnosis. Studi kami ini juga menunjukkan bahwa sepertiga dari penderita hipertensi dan hiperlipidemia tidak mendapatkan pengobatan secara adekuat. Studi ini menyimpulkan bahwa keputusan dokter untuk obat antihipertensi dan anticholesterol hanya dipengaruhi oleh tingginya tekanan darah dan kadar kolesterol itu sendiri. Sedangkan faktor risiko lainnya tidak mempengaruhi perilaku pemberian obat (peresepan). Aspek screening ini diteliti lebih lanjut pada Bab 3. Setelah hampir 6 tahun *follow-up*, kami tidak menemukan adanya efek medikalisasi pada populasi yang berpartisipasi dan yang tidak berpartisipasi dalam screening. Kami ini juga menemukan bahwa program screening akan efektif meningkatkan penggunaan obat jika dilakukan terbatas pada individu yang mempunyai risiko yang tinggi, seperti pada individu-individu yang mempunyai kadar albumin urin yang tinggi.

Aspek lain yang dibahas dalam tesis ini adalah hubungan antara penggunaan obat dengan perubahan kadar albumin urin dan fungsi ginjal. Hasil observasi yang kami lakukan menunjukkan bahwa statins berefek meningkatkan kadar albumin urin. Walaupun hasil ini tidak didukung oleh hasil uji klinik PREVEND IT, namun temuan kami ini perlu mendapat perhatian dikalangan klinisi. Studi ini juga menemukan bahwa penggunaan statins tidak berefek pada penurunan fungsi ginjal. Studi kami yang lain menemukan bahwa hormon

kontrasepsi akan meningkatkan tekanan darah, kadar albumin urin dan menurunkan fungsi ginjal, tetapi efek tersebut akan terkoreksi jika berhenti menggunakannya. Meskipun studi kami ini terbatas pada kelompok individu dengan kerusakan ginjal yang minimal, namun studi ini perlu mendapat perhatian lebih lanjut dikalangan klinisi karena kerusakan ginjal minimal merupakan awal dari gagal ginjal dan penyakit vascular. Statin dan hormon kontrasepsi sangat luas digunakan di masyarakat, sehingga hasil temuan ini sangat penting bagi 'public health' dan perlu konfirmasi studi lebih lanjut.

Apakah program screening albuminuria bisa diimplementasikan dalam praktek klinik sehari-hari? Bukti-bukti menunjukkan bahwa program screening dan terapi albuminuria akan menurunkan angka kejadian penyakit jantung dan ginjal. Hasil penelitian kami menunjukkan bahwa program screening dan terapi ini *cost-efektive*. Biaya yang diperlukan untuk meningkatkan setahun harapan hidup sebesar 16.700 EUR. *Cost-efectiveness ratio* akan lebih rendah jika terapi dilakukan pada pasien dengan kadar albumin urin lebih dari 50 mg per hari dan pasien berusia lebih dari 50 atau 60 tahun. Studi kami ini berdasarkan 'single screening program' untuk albuminuria di populasi umum. Studi lebih lanjut perlu dilakukan untuk meneliti apakah screening ulangan akan memberi keuntungan yang lebih. Markov model, suatu jenis model *cost-efectiveness* analisis sangat tepat untuk dikembangkan sebagai model simulasi untuk menilai *cost-ecektiveness* suatu program screening yang berkelanjutan di populasi umum.

PREVEND cohort studi dan IADB merupakan data set yang unik. Saat ini telah tersedia data screening tahap ketiga dari PREVEND, termasuk data morbidity dan mortality penyakit cardiovascular dan ginjal. Data peresepan obat dari seluruh farmasi juga sudah tersedia hingga akhir tahun 2005. Dengan data follow-up yang cukup lama ini (hampir 10 tahun), memungkinkan untuk dilakukannya longitudinal studi untuk meneliti lebih detail tentang hubungan antara penggunaan obat dengan penyakit-penyakit jantung dan ginjal.

Abbreviations

ACE-Inhibitor	Angiotensin Converting Enzyme - Inhibitors
ARB	Angiotensin II Receptor Blockers
ATC	Anatomical Therapeutical Chemical
ATD	Anti Thrombotic Drugs
BGLD	Blood Glucose Lowering Drugs
BMI	Body Mass Index
BP	Blood Pressure
BPLD	Blood Pressure Lowering Drugs
CABG	Coronary Arterial Bypass Grafting
CER	Cost Effectiveness Ratio
CI	Confidence Interval
CIA	Confidence Interval Analysis
CKD	Chronic Kidney Disease
CV	Cardio Vascular
CVD	Cardio Vascular Disease
CVE	Cardiovascular Events
DBP	Diastolic Blood Pressure
DDD	Defined Daily Dose
DM	Diabetes Melitus
e-GFR	Estimated-Glomerular Filtration Rate
EPIC	European Prospective Invenatigation of Cancer
ESRD	End Stage Renal Disease
GFR	Glomerular Filtration Rate
GP	General Practitioner
GREACE	GREek Atorvastatin and Coronary-heart-disease Evaluation
GRS	Groningen Random Sampling
GUIDE	Groningen University Institute for Drug Exploration
HC	Hormonal Contraceptives
HIV	Human Immunodeficiency Virus
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HOPE	Heart Outcome Prevention Evaluation
HR	Hazard Ratio
HUNT	Nord-Trodenlag Health Study
IADB	InterAction DataBase
IDDM	Insulin Dependent Diabetes Melitus
IUD	Intra Uterine Devices

LIFE	Losartan Intervention For Endpoint
LLD	Lipid Lowering Drugs
LYG	Life Year Gained
MDRD	Modification of Diet in Renal Disease
MI	Myocardial Infarction
NIDDM	Non Insulin Dependent Diabetes Melitus
NNT	Number Needed to Treat
OC	Oral Contraceptive
OTC	Over The Counter
PDD	Prescribed Daily Dose
PREVEND	Prevention of Renal and Vascular ENd-stage Disease
PREVEND-IT	Prevention of Renal and Vascular ENd-stage Disease Intervention Trial
PTCA	Percutaneus Transluminal Coronary Angioplasty
QALY	Quality Adjusted Life Year
RAS	Renin Angiotensin System
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
RR	Relative Risk
SBP	Systolic Blood Pressure
SD	Standard Deviation
SSRI	Selective Serotonin Reuptake Inhibitor
STD	Sexual Transmitted Disease
TCA	Tri Cyclic Antidepressant
UAC	Urinary Albumin Concentration
UACR	Urinary Albumin to Creatinine Ratio
UAE	Urinary Albumin Excretion
UMCG	University Medical Center Groningen
URANUS	the Use of Rosuvastatin versus Atorvastatin iN type 2 diabetes mellitUS
WHO	World Health Organization
WTP	Willingness To Pay

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List of publications

1. Atthobari J, Gansevoort RT, Visser ST, de Jong PE, de Jong-Van den Berg LTW. The effect of screening for cardio-renal risk factors on drug use in the general population. ***Submitted.***
2. Atthobari J, Gansevoort RT, Visser ST, de Jong PE, de Jong-Van den Berg LTW. The effect of hormonal contraceptives on blood pressure, urinary albumin excretion and renal function. ***Br J Clin Pharmacol (in press).***
3. Atthobari J, Brantsma AH, Gansevoort RT, Visser ST, Asselbergs FW, Gilst WH, Jong PE, Berg LT. The effect of statins on urinary albumin excretion and glomerular filtration rate: results from both a randomized clinical trial and an observational cohort study. ***Nephrol Dial Transplant. 2006 May 23;***
4. Atthobari J, Asselbergs FW, Boersma C, de Vries R, Hillege HL, van Gilst WH, Gansevoort RT, de Jong PE, de Jong-van den Berg LT, Postma MJ; PREVEND IT Study Group. Cost-effectiveness of screening for albuminuria with subsequent fosinopril treatment to prevent cardiovascular events: A pharmacoeconomic analysis linked to the prevention of renal and vascular endstage disease (PREVEND) study and the prevention of renal and vascular endstage disease intervention trial (PREVEND IT). ***Clin Ther. 2006 Mar;28(3):432-44***.
5. Atthobari J, Bos JM, Boersma C, Brouwers JR, de Jong-van den Berg LT, Postma MJ. Adherence of pharmacoeconomic studies to national guidelines in the Netherlands. ***Pharm World Sci. 2005 Oct;27(5):364-70.***
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8. Boersma C, Atthobari J, Carides GW, Postma MJ, Voors AA, de Jong-van den Berg LTW, de Jong PE, Gansevoort RT. Cost-effectiveness of losartan in patients with hypertension and LVH; results on the LIFE-study adapted to the Netherlands. *Submitted*
9. Brantsma AH, Atthobari J, Bakker SJL, de Zeeuw D, de Jong PE, Gansevoort RT. What causes progression and regression of urinary albumin excretion in the general population? *Submitted*

Curriculum vitae for Jarir Atthobari

I was born in Palembang, Indonesia on August 19th 1973. After graduating from high-school in Palembang (Sumatera, Indonesia), I moved to Yogyakarta (Central Java, Indonesia) to study medicine in Gadjah Mada University, I obtained my Bachelor of Science in 1996 and became a Medical Doctor (MD) in 1998. The title of my thesis was 'Appropriate antibiotic prophylaxis in surgical patients at Sardjito's University Hospital, Yogyakarta'. Following this, I worked as a physician in a small hospital at Bogor (West Java, Indonesia). In 2000, I commenced my Masters degree in the Department of Clinical Epidemiology and Biostatistic in Sardjito's University Hospital Yogyakarta. I did my Masters project in the Department of Pharmacology at Leopold University, Innsbruck, Austria in 2001-2002. From September 2002 until September 2006, I worked as a PhD student in the Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy (SFF) at the University of Groningen (RuG), the Netherlands. My PhD project was about drug use in population screening. This project is in collaboration with the Department of Internal Medicine, Division of Nephrology, University Medical Centre Groningen (UMCG). I was supervised by Prof. L.T.W.de Jong-van den Berg and Prof. P.E. de Jong. After completing my PhD (2006), I commenced employment in the Department of Pharmacology, School of Medicine, University of Gadjah Mada, Yogyakarta, Indonesia. My research interest involves pharmacoepidemiology, pharmacoeconomics, health economics, methodology research, as well as general clinical research.